Chapter

Existing and Newer Therapies in the Management and Diagnosis of Schizophrenia

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Abstract

Schizophrenia is a serious mental health disorder that affects a person's overall well-being. It is a functional psychosis in which severe personality changes and thought disorders occur with no evidence of organic cerebral damage. The disease manifestation primarily includes the presence of two types of symptoms "positive" and "negative." Positive symptoms include delusions, illusions, auditory hallucinations, thought disorders with irrational conclusions, poor sentence formation, and stereotypic or aggressive behavior, whereas negative symptoms include withdrawn behavior, poor socialization, emotional dampening, absence of enthusiasm, and cognitive deficits. Usually, the onset is at the age of 15–30 years. Starting treatment as early as possible is an important step in the recovery process. Cognitive symptoms include problems in attention, concentration, and memory. Antipsychotic medications can help to alleviate the frequency and intensity of psychotic symptoms. These medications are usually taken in tablet or liquid form on a daily basis. Some antipsychotic medications are given as injections at intervals of 2–4 weeks. Psychosocial treatments help people find solutions to everyday challenges and manage symptoms while attending school, working, and forming relationships. Educational programs can help family and friends learn about symptoms of schizophrenia, treatment options, and strategies for helping loved ones with the illness.

Keywords: schizophrenia, psychosis, antipsychotic medicines, hallucinations, disorganized thoughts, cognitive behavioral therapy

1. Introduction

Schizophrenia is a mental disorder characterized by disruptions in thought processes, perceptions emotional responsiveness, and social interactions. Schizophrenia is a severe and disabling disorder. It is one of the leading causes of years lost to disability worldwide.

The term schizophrenia finds its roots from "schizo" (split) and "phrene" (mind) to define the disorganized thinking of people with schizophrenia.

Characteristic presentation of the patients with schizophrenia includes symptoms such as hallucinations, delusions, and disorders in thought perception and execution,

reduced emotional expression, reduced enthusiasm to focus and achieve goals, tumultuous relationships, motor, and cognitive impairment [1].

Antipsychotic medications remain the mainstay treatment modality of schizophrenia. Evidence-based psychosocial interventions in conjunction with pharmacotherapy can help patients achieve better compliance and recovery.

Negative and positive symptoms of schizophrenia include abulia, anhedonia, social withdrawal, alogia, and affective flattening. Positive schizotypy comprises ideas of reference, delusions, illusions, and hallucinations [2].

2. Causes

The exact cause/s of schizophrenia are still unknown. Some of the postulated causes include:

Traumatic brain injury.

Childhood traumatic events.

Imbalance of the neurotransmitters, birth defects.

3. Pathogenesis of schizophrenia

3.1 Genetic predisposition

The genetic studies have provided some insights that inheritance can account for at least some proportion of schizophrenic disorders. Identical twins possess up to 60% chance of disease development. The risk in first-degree relatives is about 10% [3]. Reports of linkages of schizophrenia to loci on chromosomes 1, 2, 5, 6, 8, 10, 13, 15, and 22 have been identified [4]. Despite the evidence for genetic linkages, the results are inconclusive.

3.2 Dopamine hypothesis of schizophrenia

The dopamine hypothesis was based on the discovery that haloperidol bound to dopamine sites with higher affinity compared to the other neurotransmitters. These sites were named antipsychotic/dopamine receptor sites (D2 receptors). Subsequently, it was also established that a minimum of 65% receptor occupancy of the D2 receptors was needed for appropriate antipsychotic benefit [5].

Evidence that suggests excessive dopaminergic activity underlies the disorder:

Positron emission tomography (PET) scan shows increased dopamine (DA) receptor density in both schizophrenic patients. Post-mortem studies in the patients with schizophrenia reveal the presence of increased DA receptor densities [6].

Drugs that increase the DA activity such as levo-dopa (DA precursor) or amphetamine (DA releaser) either aggravate or precipitate symptoms of schizophrenia.

The levels of homo-vanillic acid (HVA), a metabolite of DA, in the cerebrospinal fluid (CSF), plasma, and urine increase during the early phases of therapy.

The "dopamine hypothesis" thus came into being and has been used since then to describe the underlying pathophysiology of schizophrenia.

However, in the wake of recent literature dysregulation of the serotonergic, glutamatergic, GABA-ergic, opioid, cholinergic, and probably other systems are incriminated [7].

3.3 Serotonin hypothesis of schizophrenia

According to this hypothesis, an increased excitatory neuromodulation in the serotonergic pathway in the dorsolateral frontal lobe and the anterior cingulate cortex forms an important pathophysiological basis of the disease. The concept of excessive serotonergic stimulation can also be validated by nuclear magnetic resonance (NMR) spectroscopy [8].

Additionally, the implication of serotonin as a neurotransmitter in schizophrenia stems from several observations including post-mortem human studies in patients of schizophrenia demonstrating decreased cortical 5-HT_{2A} receptor density, the psychotogenic effects of lysergic acid diethylamide (LSD) mimicking the symptoms of schizophrenia, and the ability of atypical antipsychotic drugs to bind to the serotonin receptors to bring about the antipsychotic response [8].

3.4 Glutamate hypothesis of schizophrenia

The glutamate hypothesis of schizophrenia was initially proposed based on the observation that the N-methyl-D-aspartate (NMDA) receptor antagonists like phencyclidine and ketamine induced positive and negative symptoms in healthy individuals that resembled symptoms of schizophrenia and exacerbated the symptoms in schizophrenia patients. The N-methyl-D-aspartate (NMDA) receptor is a glutamatergic receptor that may be involved in brain overactivity that is usually seen with the withdrawal of sedatives such as alcohol, resulting in agitation and seizures. Reduced glutamate receptor densities have been reported in post-mortem brains of schizophrenics [9].

Glutamate exerts excitatory and DA exerts inhibitory role over GABAergic striatal neurons which project to thalamus and serve as a sensory gate. An increase in glutamate or decrease in DA facilitates GABAergic activity at this gate. In contrast, decreased glutamate and increased DA activity will disable the gate to allow uninhibited sensory inputs to reach the cortex [10].

Additionally, studies using NMR spectroscopy neuroimaging have linked GABA and glutamate NMDA receptors to abnormal brain connectivity in individuals with schizophrenia [11].

Abnormal NMDA glutamate receptor activity is implicated in sensory and cognitive deficits, thought disorders, negative and positive symptoms of schizophrenia, and executive dysfunction [12].

4. Clinical presentation

Schizophrenia is a heterogeneous group of disorders characterized by perturbations of language, thinking, and social activity. The disorder mostly begins in the adolescent age group and has an insidious onset and a poor outcome. Social withdrawal, perceptual distortions, recurrent delusions, and hallucinations are the common presentations in the patients suffering from schizophrenia.

The manifestations of the disease include two types of symptoms: "positive" and "negative."

Patients may present with positive symptoms such as conceptual distortions, delusions, illusions, auditory hallucinations, thought disorders, garbled sentences and stereotypical aggressive behavior, delusions and hallucinations, and/or negative symptoms such as loss of functions, anhedonia, decreased emotional expression,

impaired concentration, introvert behavior, poor socialization, emotional blunting, lack of motivation, and cognitive deficits.

According to the DSM-5 criteria to diagnose schizophrenia, two (or more) of the following, each of which should be present for a significant portion of time during 1-month period (or less if successfully treated).

At least one of these must be delusions, hallucinations, or disorganized speech:

Delusions
Hallucinations
Disorganized speech (e.g., frequent derailment or incoherence)

Grossly disorganized or catatonic behavior.
Negative symptoms (i.e., diminished emotional expression or avolition).

Continuous signs of the disturbance persist for at least 6 months. This 6-month period must include at least 1 month of symptoms (or less if successfully treated) that meet the above criteria (i.e., active phase symptoms) and may include periods of prodromal or residual symptoms [13].

During these prodromal or residual periods, the signs of the disturbance may be manifested only by negative symptoms or by two or more symptoms listed above present in an attenuated form.

For a significant portion of time since the onset of the disturbance, level of functioning in one or more major areas, such as work, interpersonal relations, or self-care is markedly below the level achieved prior to the onset (or when the onset is in childhood or adolescence, there is a failure to achieve the expected level of interpersonal, academic, or occupational functioning) [13].

5. Lab investigations/neuroimaging

The neuroimaging studies have highlighted a considerable cortical tissue loss of up to 5% of the brain volume and enlargement of cerebral ventricles in the patients of schizophrenia. The affected tissue structures include the hippocampus, superior temporal, and the prefrontal cortex which are also present with reduced gray matter volumes [14].

Hyperactivity in the hippocampal and the dorsal lateral prefrontal cortex regions has been observed in various MRI studies, leading to a postulation that a loss of inhibitory functions of the neurons may be responsible to an extent for the symptoms in schizophrenia.

A plentitude of structural and functional imaging modalities is currently being contemplated to discern the patterns of brain connectivity particularly to outline the factors that cause a transition to full-blown psychosis [15].

6. Differential diagnosis

It is impertinent to diagnose and delineate schizophrenia from a wide range of mental disorders, including but not limited to:

- Substance-induced psychotic disorder
- Mood disorders with psychotic features

- Sleep-related disorders
- Delusional disorder
- Paranoid personality disorder
- Schizotypal personality disorder
- Pervasive developmental disorder
- Psychosis secondary to organic cause

7. Management of schizophrenia

7.1 Non-pharmacological

A range of effective care options for people with schizophrenia exists including cognitive behavioral therapy, medication, psychoeducation, and psychosocial therapy.

Facilitated and assisted living, societal support systems, and employment environments are quintessential care options for patients living with schizophrenia.

A recovery-oriented treatment practice, that is, giving people the agency in treatment decisions, is crucial for people with schizophrenia and their guardians.

7.2 Pharmacological

Antipsychotic medications remain the cornerstone in the management of schizophrenia. They are thought to control psychotic symptoms by affecting the level of neurotransmitter dopamine in the brain.

The treatment goal is to manage signs and symptoms at the lowest possible dose. Different drugs, different doses, or combinations can be implemented over time to achieve the desired result. Other symptoms accompanying psychosis could be addressed with medications such as anti-depressants or anti-anxiety drugs. It can take several weeks to notice an improvement in symptoms.

The Texas Medication Algorithm Project (TMAP) entails a six-stage pharmacotherapeutic algorithm in the treatment of schizophrenia.

Stage 1 involves treatment initiation with a second-generation antipsychotic (SGA) as a first-line therapy. In case of little to no therapeutic response, proceed to stage 2.

Stage 2 includes monotherapy with either another SGA or a first-generation antipsychotic (FGA). In case of absence of any therapeutic response, proceed to stage 3.

Stage 3 consists of clozapine monotherapy with a constant monitoring of the white blood cell (WBC) count. In case of agranulocytosis, clozapine therapy should be suspended. In case of absence of therapeutic response in stage 3, proceed to stage 4.

Stage 4 entails a combination of clozapine therapy with an FGA or an SGA or electroconvulsive therapy (ECT). In case of resistance to treatment, proceed to stage 5.

Stage 5 calls for monotherapy with an FGA or an SGA that has not been tried. Finally, in case of stage 5 treatment is still unsuccessful, proceed to stage 6.

Stage 6 consists of combination therapy with an SGA, an FGA, ECT, and/or a mood stabilizer.

Combination therapy is recommended only in the later stages of the treatment algorithm [16].

Due to an increased predisposition to cause drug interactions, treatment nonadherence, and medication errors, routinely prescribing two or more antipsychotics is not endorsed.

8. Choice of antipsychotic medication

The choice between typical (FGA) and atypical antipsychotic (SGA) is of paramount importance.

As per the American Psychiatric Association, second-generation or the atypical antipsychotics (SGAs) except for clozapine are the agents of first choice in the treatment of schizophrenia. SGAs are usually preferred over first-generation antipsychotics (FGAs) because of their disposition for lesser extrapyramidal symptoms [17].

The clinical potencies of typical antipsychotic drugs are proportional to their respective affinities for the dopaminergic D2 receptor. The available antipsychotic agents are effective in only up to 70% of patients presenting with a first episode and full remission of symptoms may take up to 6–8 weeks. Appropriate clinical and drug history of the patient should be taken to help delineate and commence treatment with a new antipsychotic agent.

Lack of response to an antipsychotic drug for at least 6–8 weeks with good compliance should mandate a change in the antipsychotic.

Clozapine needs to be considered after failure of sequential trials of two antipsychotics (one of which is an SGA) or if the patient has an aggressive behavior, suicidal tendencies, not responding to their prescribed antipsychotic medication, and those experiencing unbearable side effects with two different classes of antipsychotic medications.

First-generation or typical antipsychotics are better suited to treating positive symptoms of schizophrenia, whereas the newer agents appear to be more effective in handling the positive and the negative as well as improving the cognitive symptoms.

Long-acting injectable preparations (risperidone, paliperidone, olanzapine, and aripiprazole) are considered when there is noncompliance with the therapy.

9. Treatment-resistance

Up to 30% of patients with schizophrenia show only little symptomatic improvement or unacceptable side effects after multiple trials of FGAs therapy. Clozapine is the most effective oral antipsychotic in terms of managing treatment-resistant schizophrenia.

10. First-generation antipsychotics

The first-generation antipsychotics have numerous and serious neurological side effects, that may or may not be irreversible. First-generation antipsychotics include:

- Chlorpromazine
- Fluphenazine
- Haloperidol
- Pimozide
- Sulpiride
- Perphenazine

11. Second-generation antipsychotics

These groups of newer generation medications are chosen as they possess a lower risk of serious side effects compared to the first-generation antipsychotic agents. Second-generation antipsychotics include:

- Aripiprazole
- Asenapine
- Brexpiprazole
- Cariprazine
- Clozapine
- Iloperidone
- Lurasidone
- Olanzapine

- Paliperidone
- Quetiapine
- Risperidone
- Ziprasidone

12. Long-acting injectable antipsychotics

In patients where non-adherence due to pill burden or side effects to oral medications is an impedance, some long-acting injectable antipsychotics can be given as intramuscular or subcutaneous injections. Depending on the medication they are usually given once every 2–4 weeks.

Common medications that are available as an injection include:

- Aripiprazole
- Fluphenazine decanoate
- Haloperidol decanoate
- Paliperidone
- Risperidone

13. Antipsychotic treatment

13.1 Dose

The dose of the antipsychotic needs to be tailored for every patient. A fine balance between relapse prevention and reducing the side effects should be maintained. Patients not experiencing positive symptoms during therapy may be candidates for reduction in doses, while monitoring for potential relapse. According to literature the dose of the medication needs to be tapered gradually by about 20% every 6 months till a stable effective dose is reached [18].

13.2 Duration of treatment

The duration of treatment depends on a number of factors and should be personalized. The suggested guidelines are as follows:

- First-episode patients ought to receive 1–2 years of maintenance treatment.
- Patients with several episodes or exacerbations are to receive maintenance treatment for 5 years or longer after the last episode.
- Patients with a history of suicide attempts or showcasing aggressive behavior should receive treatment for longer time periods.

Rapid initiation of drug treatment is of utmost importance, specifically within the first 5 years after an acute episode, as this is the duration where most neurological changes in the brain take place [19].

13.3 Augmentation and combination therapy

In case of inadequate or subtherapeutic response to clozapine therapy in the patients both the augmentation (i.e., ECT and or a mood stabilizer) and combination therapy (with another antipsychotic) may be considered.

However, exposure to multiple antipsychotics at the same time may increase the risk of serious side effects [20].

The practicing physicians should contemplate the following factors before administering the augmentation therapy: [21].

- The augmentation therapy should be considered in patients with a prior inadequate or subtherapeutic response to therapy.
- Augmentation agents are effective in treating symptoms of schizophrenia when given in conjunction with other treatment modalities.
- In case of lack of clinical response to the augmentation strategy, the therapy should be withheld and other options should be contemplated.

Mood stabilizers, anxiolytics, anti-depressants, and anti-convulsant are commonly used as drugs in the augmentation therapy [22].

Treatment during the acute phase of schizophrenia is followed by a maintenance phase of treatment which aims at increasing socialization and improving self-care and mood.

Maintenance treatment is essential to help prevent relapse of symptoms. In most schizophrenia patients, it is difficult to implement effective rehabilitation programs without using antipsychotic agents [19].

14. Mechanism of drug action

The exact mechanism by which the antipsychotic drugs produce their effects remains obscure. Depending on their receptor affinities, they are mainly categorized as follows:

1. Typical or older antipsychotic agents, which produce their therapeutic effects primarily via high dopamine (D_2) antagonism and low serotonin ($5\text{-}HT_{2A}$) antagonism;
2. The therapeutic efficiency of atypical neuroleptics, revolves around the antagonism of the N-methyl-D-aspartate (NMDA) and α1 and α2 adrenergic activity, thereby modifying the balance between 5-HT2 and D2 receptor activity. These agents demonstrate moderate to high D_2 and 5-HT2A receptor antagonism [23].

To contain the positive symptoms of schizophrenia, at least 60–65% of D_2 receptors must be occupied by the antipsychotic agents, whereas ≥77% of D_2 receptor blockade has been associated with the extrapyramidal symptoms [23].

The improvement in the negative paradigms of schizophrenia and the cognitive benefits with the use of atypical antipsychotics has been attributed primarily to the 5-HT_{2A} antagonism in combination with the D_2 antagonism, resulting in the release of dopamine into the prefrontal cortex [17].

15. Side effects of the antipsychotic drugs

15.1 Endocrine system

Hyperprolactinemia has been seen to occur in up to 80% of patients treated with antipsychotic agents like risperidone or paliperidone, which may lead to sexual dysfunction, decreased libido, menstrual irregularities, or gynecomastia. Some of the newer atypical antipsychotic agents like aripiprazole or ziprasidone may serve as possible replacement treatment options in the patients with increased prolactin levels [24].

Weight gain is another significant side effect in patients receiving antipsychotic drugs and may eventually lead to non-adherence.

Antipsychotic drugs also can increase the risk of type-II diabetes. Olanzapine has the greatest risk of diabetes, followed by risperidone and quetiapine [24].

15.2 Cardiovascular system

Orthostatic or postural hypotension and tachycardia are attributed to the α1 adrenoceptor blockade and vagal inhibition, respectively. These have been seen to occur in up to 75% of patients treated with an antipsychotic agent. Patients with diabetes, pre-existing cardiovascular disease, or elderly age appear to be at a greater risk, and counseling regarding the same should be practiced [17].

ECG changes, especially QTc prolongation, can occur with the use of antipsychotic agents such as thioridazine, clozapine, iloperidone, and ziprasidone. QTc prolongation should be constantly monitored throughout the therapy, and treatment must be discontinued if this interval consistently exceeds 500 msec. The choice of an antipsychotic agent should be based on the patient profile taking into consideration patients' pre-existing cardiac or cerebrovascular disease or the use of drugs like diuretics or the drugs that have a tendency to prolong the QTc interval [17].

15.3 Lipid changes

Hypertriglyceridemia, hypercholesterolemia, and dyslipidemia are a possible squeal in the patients of schizophrenia treated with SGAs or typical antipsychotics like phenothiazines. Newer antipsychotics that are safer in this regard include drugs such as risperidone, ziprasidone, and aripiprazole. Olanzapine has been shown to have negative effects on cholesterol levels and lipids [21].

15.4 Central nervous system

15.4.1 Dystonia

This disorder often results in non-adherence and can be life-threatening. Dystonic reactions typically accompany treatment with FGAs. Dystonia may be minimized by using SGAs or by initiating FGAs at lower doses [17].

15.4.2 Akathisia

Akathisia is an inability to remain still and has been seen in up to 40% of patients treated with high-potency older antipsychotic agents such as haloperidol and fluphenazine. Novel antipsychotics such as quetiapine and clozapine appear to have the lowest risk for this side effect. The use of propranolol and diphenhydramine may be helpful in providing relief in this regard [25].

15.4.3 Pseudoparkinsonism

The incidence of this disorder has ranged from 15% to 36% in patients treated with FGAs. There is an increased risk of drug induced Parkinsonism with higher doses of risperidone. Although the incidence of the same taking into consideration, the use of novel antipsychotics in the treatment of schizophrenia-increased risk is relatively low. Treatment of drug-induced Parkinsonism is with the use of anti-cholinergic agents such as trihexyphenidyl and procyclidine [17].

15.4.4 Tardive dyskinesia

Characterized by involuntary oro-buccal-lingual dyskinesias. The prevalence of the disorder is up to 25% among patients receiving FGA therapy. The risk of tardive dyskinesia is significantly lower with the use of newer generation antipsychotic agents. The management of tardive dyskinesias involves increasing the cholinergic activity along with "neurolept-holidays" [17].

15.4.5 Sedation

Chlorpromazine, thioridazine, mesoridazine, clozapine, olanzapine, and quetiapine have the highest sedation potential. The potential of these agents could be exploited in patients of schizophrenia accompanied by irritation and insomnia. Studies have shown that SGAs offer superior cognitive benefits compared with FGAs [17].

15.4.6 Seizures

All antipsychotic agents carry an increased predisposition to cause seizures. The antipsychotic agents that are the most infamous for causing seizures are clozapine and chlorpromazine. Antipsychotic agents including risperidone, molindone, thioridazine, haloperidol, pimozide, trifluoperazine, and fluphenazine are associated with the lower risk in this regard.

15.4.7 Poikilothermia

One of the severe side effects of antipsychotic therapy is poikilothermia. Patients may be at increased risk of heat stroke because of the inability to dissipate excess body heat, especially during exercise or physical exertion. These side effects most commonly occur during treatment with the older antipsychotics such as chlorpromazine, but they have also been associated with the SGAs such as clozapine [17].

15.4.8 Neuroleptic malignant syndrome (NMS)

It is a life-threatening side effect of antipsychotic drug therapy in extremely sensitive to the extrapyramidal side effects of neuroleptics. The incidence of NMS is up to 1.0% in the patients treated with the older antipsychotics such as fluphenazine and haloperidol. The novel antipsychotic agents appear to be relatively safer in this regard. The treatment of NMS involves the use of drugs such as dantrolene, diazepam, and bromocriptine [17].

15.4.9 Miscellaneous adverse effects

Schizophrenia medications can cause a variety of other adverse effects, including the following:

- Chlorpromazine is commonly associated with opaque deposits in the lens.
- Quetiapine is associated with an increased risk of cataracts. Whereas, thioridazine at doses ≥800 mg daily is at risk of retinitis pigmentosa.
- Clozapine has been associated with urinary hesitancy and retention.
- FGAs and risperidone have a greater tendency to cause sexual dysfunction.
- Treatment with antipsychotics can cause transient leukopenia.
- Clozapine, chlorpromazine, and olanzapine are associated with a risk of hematological complications such as neutropenia or agranulocytosis.
- Both FGAs and SGAS can cause photosensitivity reactions.

The varying safety profiles of antipsychotic medications may be due to their effects on various neuroreceptor systems.

16. Progress evaluation

The progress of recovery during the treatment of schizophrenia is both objective and subjective.

Objectively, the recovery can be quantified by the relief of symptoms and the return of the patient to work. The use of various scales including the Brief Psychiatric Rating Scale (BPRS) and the Positive and Negative Syndrome Scale (PANSS) serve as valuable pointers in the improvement of schizophrenia.

Subjective parameters of recovery are measured by the patient themselves in terms of his or her life satisfaction, feeling of hope, and knowledge about his or her mental illness [26].

Despite continuous recent therapeutic advances into the treatment, there is a significant number of years lost to disability and a substantial reduction in life expectancy in the patients suffering from schizophrenia by about 10–25 years [26].

17. Antipsychotic drugs

17.1 Typical antipsychotic drugs (older generation antipsychotic drugs)

17.1.1 Butyrophenone

Butyrophenones are synthetic compounds employed as antipsychotic medications. Besides treating psychotic conditions, certain members have demonstrated effectiveness in controlling nausea and vomiting. A few examples within this class include haloperidol, droperidol, melperone, domperidone, and benperidol.

17.1.2 Haloperidol

Haloperidol, a widely used first-generation typical antipsychotic, is used to address the positive symptoms of schizophrenia. It blocks the dopaminergic D2 receptors in the brain. It reaches its peak effectiveness at 72% receptor blockade. However, besides blocking the D2 receptors, haloperidol also blocks the noradrenergic, cholinergic, and histaminergic receptors, which amount to several adverse drug reactions.

17.1.2.1 Pharmacokinetics

Absorption: Haloperidol is a highly lipophilic drug, and its oral bioavailability is 70%. The time to reach peak plasma concentration is 6 hours after oral administration. It is approximately 93% plasma protein bound. It undergoes extensive metabolism in the liver via sulfoxidation and CYP3A4, 2D6, and 1A2 enzymes [27].

Approximately 30% of haloperidol is primarily excreted in the urine.

Schizophrenia: The recommended dosing involves oral administration of 5–20 mg, taken 2–3 times a day. The maximum recommended oral dosage should not exceed 100 mg/d.

17.1.2.2 Extrapyramidal adverse effects

Acute dystonia, akathisia, neuroleptic malignant syndrome (NMS), Parkinsonism, and tardive dyskinesia (TD) are commonly observed in haloperidol therapy.

Other less common adverse effects include orthostatic hypotension, lens opacities, anxiety, cerebral edema, depression, dizziness, confusion, anorexia, constipation, dyspepsia, ileus, QT prolongation, and torsades de pointes [28].

17.1.3 Pimozide

Pimozide is commonly used as an antipsychotic agent. It works by affecting the balance of certain neurotransmitters in the brain, helping to alleviate symptoms of delusions and hallucinations.

17.1.3.1 Pharmacokinetics

Pimozide is well-absorbed orally and reaches peak concentrations within a few hours. It is widely distributed throughout the body, including the central nervous system (CNS). It is metabolized through the CYP450 enzyme system. Its long half-life leads to a sustained duration of action. The drug and its metabolites are excreted in the feces, with a smaller portion excreted in the urine.

17.1.3.2 Dosage

The dosage of pimozide is usually started from 1 to 2 mg/day.

17.1.3.3 Adverse reactions

Changes in prolactin levels, menstrual irregularities, and blood dyscrasias. Neuroleptic malignant syndrome, QTc prolongation, sedation, drowsiness, affecting alertness and concentration dry mouth, constipation, urinary retention, blurred vision, and weight gain.

Extrapyramidal symptoms including tremors, rigidity, bradykinesia, tardive dyskinesia are seen with the use of pimozide.

17.1.4 Phenothiazines

17.1.4.1 Chlorpromazine

Chlorpromazine belongs to the first-generation antipsychotic (FGA) or typical antipsychotics. It exerts its antipsychotic effect by blocking post-synaptic D2 receptors in the mesolimbic pathway. However, its extrapyramidal side effects are attributed to the blockade of D2 receptors in the nigrostriatal pathway. The antiemetic effect of chlorpromazine is attributed to the combined blockade of histaminergic H1, dopaminergic D2, and muscarinic M_1 receptors in the vomiting center.

17.1.4.2 Pharmacokinetics

Chlorpromazine is metabolized primarily by the CYP1A2 and 2D6 enzymes. Elimination takes place through urine, bile, and feces, with a half-life ranging from 10 to 40 hours for its active metabolite.

The medication is available as tablets and can also be administered as intramuscular and intravenous injections.

17.1.4.3 Dosage

The dose is initially started from 25 to 75 mg/day orally twice a day to a range of 100–1000 mg/day.

The parenteral route of the drug is initially started at 25 mg, followed by 25–50 mg after 1–4 hours. The usual dose can be up to 800 mg/day.

17.1.4.4 Adverse drug reactions (ADRs)

It causes non-neurologic side effects such as dryness of mouth, blurring of vision, dizziness, postural hypotension, urinary retention, and constipation by blocking the muscarinic receptors. Elderly age patients are particularly at an increased risk of angle-closure glaucoma. Due to the blockade of the histamine H1 receptors, there is an increased potential for sedation.

It also causes hyperprolactinemia, gynecomastia, galactorrhea, erectile dysfunctions irregular menstruation, oligomenorrhea, amenorrhea, and galactorrhea.

Corneal depositions, QT interval prolongation, cholestatic jaundice, and drug induced hepatotoxicity, which may significantly increase the alanine

aminotransferase level (ALT). Regular monitoring of the liver enzymes should be done during chlorpromazine therapy, and in case of the early detection of liver injury, the drug should be stopped.

Chlorpromazine can also cause EPS such as acute dystonia, akathisia, Parkinsonism, and tardive dyskinesia (TD) [29].

17.1.5 Thioridazine

It is a typical antipsychotics used to effectively treat the positive symptoms of schizophrenia, such as hallucinations, delusions, and disorganization by blocking D2 receptors in the mesolimbic pathway. Thioridazine is a substrate of the hepatic enzyme CYP450 2D6 and is also an inhibitor of the same enzyme.

17.1.5.1 Dosage

Thioridazine is initiated from 50 to 100 mg three times per day to a maximum of 800 mg/day.

17.1.5.2 ADRs

17.1.5.2.1 Extrapyramidal side effects

It is associated with a risk of developing EPS including dystonia, Parkinsonism, and tardive dyskinesia. The neuroleptic malignant syndrome (NMS) is another serious side effect.

Thioridazine is associated with prolonged QTc intervals, such as torsades de pointes. Hence, initiating this medicine at a lower dose is advised, and a prior ECG should be done.

Pigmentary retinopathy is specific to thioridazine. Nonspecific symptoms include dry mouth, dry eyes, sedation, orthostatic hypotension, weight gain, dizziness, erectile dysfunction, pruritus, photosensitivity, and constipation. Rare ADRs include irreversible retinal pigmentation, poikilothermia, and agranulocytosis [29].

17.1.6 Fluphenazine

Fluphenazine is a high-potency antipsychotic agent which brings about its therapeutic effect largely through antagonism of post-synaptic D-2 dopaminergic receptors in mesolimbic, nigrostriatal, and the tuberoinfundibular pathways. The blockage of post-synaptic dopaminergic D-2 receptors in the mesolimbic pathway addresses the positive symptoms of schizophrenia.

Owing to the antagonistic actions on the α1 adrenergic receptors, fluphenazine is known to cause various cardiac side effects. Fluphenazine has strong antagonistic effects at both muscarinic M-1 and histaminergic H-1 receptors.

17.1.6.1 Dosage

Fluphenazine is typically initiated from 2.5 to 10 mg/day divided every 6 to 8 hours.

Fluphenazine has a relatively half-life of about 15 hours. The injection formulations are dosed from 12.5 to 25 mg I.M. or S.C. every 28 days. The maximum dose of fluphenazine is 40 mg/day.

17.1.6.2 Pharmacokinetics

It is extensively metabolized and undergoes "first pass" metabolism in the hepatocytes and is excreted both via the urinary and fecal route. It is ≥90% plasma protein bound. With oral fluphenazine, peak plasma/serum levels are attained within a few hours. Fluphenazine crosses the blood-brain barrier and the blood-placental barrier easily and cannot be removed by dialysis.

17.1.6.3 ADR

Due to the dopamine receptor antagonism as well as its anticholinergic antihistaminic and alpha receptor blocking actions, fluphenazine has a wide range of adverse effect profile. Fluphenazine is commonly associated with sedation, dryness of mouth and eyes, blurring of vision, urinary retention and constipation, orthostatic hypotension, reflex tachycardia, and dizziness. Extrapyramidal side effects including akathisia, pseudo-parkinsonism and tardive dyskinesia are also observed [30].

Endocrinal side effects such as galactorrhea, gynecomastia, sexual dysfunction, amenorrhea in females, and on off-cycle bleeding can occur. Various serious side effects including neuroleptic malignant syndrome, liver function abnormalities, jaundice, seizures, and agranulocytosis have been observed. It carries a black-box warning for increased risk of cerebrovascular events and death especially in the elderly patients. QT interval prolongation and T-wave abnormalities have been also been associated with its use [30].

17.1.7 Thioxanthenes

17.1.7.1 Flupentixol

It is a typical antipsychotic drug of the thioxanthene class.

Although commonly prescribed as an oral tablet formulation, it is mainly used is as a long-acting injectable formulation that can be given once or twice a month to individuals with schizophrenia having poor compliance and adherence with the oral medications and/or a history of frequent relapses.

17.1.7.2 Pharmacokinetics

It is absorbed 40% after oral administration. It is widely distributed throughout the body including the CNS. It is 99% plasma protein bound. It is extensively metabolized. The metabolites are excreted in the feces and urine. The dihydrochloride metabolite has a half-life of 35 hours.

The dose range of flupenthixol varies from 10 to 200 mg/2 to 4 weeks.

17.1.7.3 Adverse drug reactions

Hypokinesia, muscle rigidity, Parkinsonism, tremors, akathisia, dystonia, dry mouth, dizziness, blurring of vision, agranulocytosis, and osteoporosis on long-term use [31].

17.1.8 Sulpiride

Sulpiride is an antipsychotic medication that belongs to the benzamide class. Sulpiride exerts its therapeutic effects by blocking dopamine D2 and D3 receptors.

17.1.8.1 Pharmacokinetics

Following oral administration, it has a bioavailability of 30%. It is approximately 40% plasma protein bound particularly to albumin. It is has a plasma half-life around 8 hours. It has an aVD of about 2.72 ± 0.66 L/kg.

17.1.8.2 Dosage

The usual dosage is started from 4 mg twice a day.

Side effects include extrapyramidal symptoms, sedation, weight gain, dyslipidemia, and hyperprolactinemia [32].

17.2 Atypical neuroleptics

17.2.1 Clozapine

It is a second-generation or atypical antipsychotic. It acts as an atypical antipsychotic to dopamine and serotonin receptors. It binds to the 5-HT1A and D4 receptor more than the D2 receptor, contributing to decrease adverse events and extrapyramidal symptoms. Unlike other antipsychotics, clozapine does not cause a rise in prolactin level.

17.2.1.1 Pharmacokinetics

The peak concentrations are attained in 2.5 hours. It exhibits approximately 97% plasma protein binding. The uptake of clozapine in the liver is by solute carrier family (SLC) transporter protein. Clozapine is metabolized by CYP3A4. It has a half-life up to 12 hours. Approximately 50% of clozapine is excreted in the urine and 30% in the feces.

Treatment is started from 12.5 mg once or twice daily and increased by 25–50 mg daily to target 150–600 mg daily in divided doses by day 14.

17.2.1.2 Adverse effects

Agranulocytosis mandating weekly WBC count especially for first 3 months of therapy, myocarditis, metabolic syndrome, hyperglycemia, hypertriglyceridemia, seizures, excessive salivation, pulmonary embolism, and neuroleptic malignant syndrome [33].

17.2.2 Olanzapine

Olanzapine is a second-generation (atypical) antipsychotic medication. It works as D2 receptor antagonist at the post-synaptic receptors leading to a decrease in positive symptoms in patients, including hallucinations, delusions, disorganized speech, thoughts, and behavior. Olanzapine is similar neurochemically to clozapine but has a significant risk of inducing weight gain.

Olanzapine works similarly on serotonin 5HT2A receptors in the frontal cortex as an antagonist and decreases negative symptoms, including anhedonia, flat affect, alogia, avolition, and poor attention.

17.2.2.1 Pharmacokinetics

Absorption: Steady-state plasma concentration in about 1 week. The time to peak concentration is 6 hours for oral formulation. The volume of distribution is approximately 1000 L, and it is 93% plasma protein bound.

Olanzapine is extensively metabolized by glucuronidation and the cytochrome P450 system primarily CYP1A2 and 2D6. The half-life of olanzapine is approximately 30 hours. Olanzapine is excreted primarily via the renal route (57%) and feces (30%).

The usual dosage is started from 2.5, 5, 7.5, 10, 15, and 20 mg dosages to targeted 10–30 mg/day.

17.2.2.2 Adverse drug reaction

Impaired glucose tolerance, metabolic syndrome, increased akathisias, and extrapyramidal symptoms [34].

17.2.3 Risperidone

It exhibits their therapeutic effects through some D2 and 5HT2A blockade. Their binding affinity to the D2 receptors is low accounting for the lesser likelihood of causing EPS. The relative potency is more toward the 5-HT2 receptor sites than the D2 receptor sites. Risperidone also exerts considerable α2 antagonism.

Paliperidone is a recently approved agent that is a metabolite of risperidone and shares many of its properties.

They are agonist at the 5HT1A receptor, besides it also has additional serotonin and norepinephrine reuptake inhibiting effects. The blockade of the D2 receptors specifically in the mesolimbic pathway is thought to be the reason for the improvement in the positive symptoms of schizophrenia.

The dosage is started from 1 mg daily, to a maximum dose of 16 mg daily.

17.2.3.1 ADR

Acute dystonia, akathisia, tardive dyskinesia, weight changes, metabolic changes, and sedation are significant concerns with risperidone [35].

17.2.4 Quetiapine

Quetiapine has many complex mechanisms, but it mediates its pharmacological effect via its 5HT2 antagonistic action. Quetiapine has a strong affinity for the 5-HT2 and on the dopaminergic D1 and D2 receptors, where they act as an antagonist to bring about the therapeutic response. Additionally, it has anxiolytic and antidepressant properties owing to the blockade of the norepinephrine transporter (NET) and partial agonistic activity at the 5 HT1A receptor, respectively. Quetiapine is distinct in having a weak D2 effect but potent α1 and histamine blockade.

The usual dose is 300–800 mg/day. The half-life for quetiapine is about 7 hours.

17.2.4.1 Adverse drug reactions

It is associated with an increased risk of death in dementia-related psychosis in elderly patients. Neuroleptic malignant syndrome, increased suicidal ideations, somnolence, orthostatic hypotension, and dizziness are the most common side effects of quetiapine [36].

17.2.5 Ziprasidone

Ziprasidone is another atypical antipsychotic agent that has a substantial binding affinity for the 5HT2A receptors compared to the D2, α1, and H1 receptors.

Antagonism at the dopamine (D2) receptor in the mesolimbic pathway may be responsible in diminishing the positive symptoms, whereas the antagonism at the 5HT2A receptor sites in the mesocortical pathway may be responsible for the reduction of negative symptoms of psychosis. Ziprasidone causes minimal weight gain and is unlikely to increase prolactin but may increase QT prolongation.

17.2.5.1 Pharmacokinetics

Ziprasidone has a half-life of 7–10 hours. It attains its steady-state plasma concentration within 1–3 days of initiation of dosing. The average systemic clearance of ziprasidone is 7.5 ml/min/kg. Elimination of ziprasidone is primarily via the hepatic route.

17.2.5.2 Dosage

Ziprasidone is started at 20 mg twice per day with meals, to a maximum of 120–200 mg/day. As several days are needed to attain steady-state plasma concentrations, dose adjustments should occur gradually after a few days.

17.2.5.3 ADR

Patients treated with antipsychotic drugs may develop tardive dyskinesia [37].

17.2.6 Aripiprazole

Aripiprazole, an atypical antipsychotic, has shown effectiveness in reducing irritability, hyperactivity. Acting as a partial agonist at D2 and 5HT-1a receptors and an antagonist at the 5HT-2a receptor. Aripiprazole stabilizes dopamine and serotonin in specific brain regions, effectively managing positive, negative, and cognitive symptoms in schizophrenia.

17.2.6.1 Pharmacokinetics

Aripiprazole has an oral availability is 87%. The mean elimination half-life is about 75 hours. Aripiprazole acts as a substrate of both the cytochrome P-450 3A4 and 2D6 isoenzymes, predisposing to various drug-drug interactions.

Dosage aripiprazole should be started at a dose of 10 or 15 mg/day, preferably administered along with the meals. The maximum dose should not exceed 30 mg/day.

17.2.6.2 ADR

The most frequent adverse effects are headache, anxiety, insomnia, nausea, vomiting, lightheadedness, weight gain, or prolactin increase as a result of its partial agonist properties [38].

17.2.7 Zotepine

Zotepine is an antipsychotic medication used in the treatment of various psychiatric disorders, primarily schizophrenia.

17.2.7.1 Pharmacokinetics

Zotepine is typically administered orally, and its absorption may be influenced by factors such as the formulation of the drug and the individual's gastrointestinal function. After absorption, it is distributed throughout the body, including the central nervous system, where it exerts its therapeutic effects. It undergoes metabolism in the liver, through the cytochrome P450 system. Zotepine and its metabolites occurs through renal excretion and possibly through hepatic routes.

17.2.7.2 Dosage

25 mg tid increased at 4-day interval to a maximum of 100 mg tid.

17.2.7.3 Adverse reactions

Common side effects of zotepine may include sedation, weight gain, orthostatic hypotension, and anticholinergic effects such as dry mouth. Metabolic effects, including changes in blood glucose and lipid levels, are also seen with its use [39].

17.2.8 Sertindole

Sertindole is an atypical antipsychotic medication. It works by blocking the dopaminergic and serotonin receptors which helps to normalize the imbalance of these neurotransmitters associated with psychotic disorders.

17.2.8.1 Pharmacokinetics

Sertindole is typically administered orally, and its absorption may be influenced by factors such as the formulation of the drug and individual variations in gastrointestinal function. After absorption, sertindole is likely to be distributed throughout the body, including the central nervous system, where it exerts its therapeutic effects. Sertindole undergoes extensive hepatic metabolism, primarily through the cytochrome P450 enzyme system. The elimination of sertindole and its metabolites primarily occurs through renal excretion and possibly through hepatic routes.

17.2.8.2 Dosage

Initially started with 4 mg/day to a maximum of 24 mg/day.

17.2.8.3 Adverse reactions

Common side effects may include sedation, weight gain, increased appetite, orthostatic hypotension, and QT interval prolongation [40].

17.2.9 Asenapine

It is an atypical antipsychotic medication that is used for the treatment of schizophrenia and bipolar disorder.

17.2.9.1 Pharmacokinetics

Absorption: It is formulated for sublingual administration. The sublingual route allows for rapid absorption and onset of action. It is extensively plasma protein bound. It undergoes hepatic metabolism, through the cytochrome P450 (CYP) enzyme system. The elimination half-life of asenapine is relatively short, and it is eliminated through both hepatic and renal routes.

Drug Interactions: Asenapine may interact with other medications that are strong inhibitors or inducers of CYP1A2 and CYP2D6 influencing their plasma concentrations.

Dosage: Asenapine is typically administered sublingually in doses of 5–10 mg twice daily.

Adverse reactions: Common side effects may include sedation, somnolence, weight gain, metabolic effects, orthostatic hypotension, and increased blood glucose levels. It is also associated with a risk of extrapyramidal side effects [41].

17.2.10 Lurasidone

Lurasidone is an atypical antipsychotic. The mechanism of action of lurasidone involves both the dopaminergic and serotonergic receptors. It acts as an atypical antipsychotic owing to the antagonism at the D2, 5-HT2A receptors, whereas antagonism at the 5-HT7 and partial agonism at the 5-HT1A receptors contribute to the antidepressant properties of lurasidone.

17.2.10.1 Dosage

Lurasidone is available in various strengths, that is, 20, 40, 60, 80, and 120 mg tablets. It is poorly soluble after oral ingestion. It should be administered with a slightly high calories diet, regardless of the fat content, which helps in increasing its oral bioavailability. Upon administration the time to peak plasma concentration takes about 3 hours, and a steady-state concentration is achieved in 7 days. Lurasidone is primarily metabolized by CYP3A4 isoenzyme.

Usually started from 40 mg/day to a maximum dose of 160 mg/day in adults and 80 mg/day in adolescents. In the case of renal and hepatic impairment, the maximum dose is 80 mg/day.

17.2.10.2 Adverse effects

Lurasidone is a relatively safety advantage with a reduced risk of metabolic side effects such as hypercholesterolemia, hyperlipidemia, hyperglycemia, and weight gain when compared with the other atypical antipsychotic agents.

The most common adverse effects experienced are nausea, akathisia, somnolence, weight gain, sedation, and drug-induced Parkinsonism [42].

18. Newer approaches

18.1 Ulotaront

Ulotaront (SEP-363856) is a trace-amine-associated receptor 1 (TAAR1) agonist having a 5-HT1A receptor agonist activity. It is in phase III clinical development, with FDA breakthrough therapy designation, for the treatment of schizophrenia. Population-based pharmacokinetic analysis showed that ulotaront was rapidly absorbed and quickly cleared from plasma after oral administration to subjects with schizophrenia. The plasma protein binding of ulotaront is relatively low. It has been shown to inhibit CYP2D6, and it induces CYP2B6 [43].

18.2 Ralmitaront

Ralmitaront (RO6889450) is a TAAR1 partial agonist presently undergoing phase II clinical trials.

Further results are awaited.

18.3 KarXT (xanomeline-trospium)

Xanomeline is a dual M_1 and M_4 muscarinic receptor agonist having negligible D_2 dopamine receptor blockage, which is unlike the presently available therapies for schizophrenia. Xanomeline-trospium (KarXT) combines xanomeline with the peripherally restricted muscarinic receptor antagonist trospium chloride with the goal of improving xanomeline-related adverse events associated with peripheral muscarinic receptors. In the phase III EMERGENT-2 trials, it has been shown to decrease positive and negative symptoms of schizophrenia [44].

18.4 Emraclidine (CVL-231)

Emraclidine is a novel, brain-penetrant, highly selective M_4 receptor positive allosteric modulator in development for the treatment of schizophrenia. It is presently in phase II clinical trials. M_4 receptor subtypes are selectively expressed in the striatum and activation of these receptors has been shown to indirectly regulate dopamine levels without blocking D2/D3 receptors, which may lead to unwanted motor side effects seen in current antipsychotics [45].

18.5 Pimavanserin

It is a selective serotonin receptor-modulating agent with a preferable inverse agonist/antagonist activity at serotonergic 5-HT_{2A} receptors. Steady-state C_{max} and $AUC_{0–24}$ values are approximately 3- to 5-fold greater after once-a-day oral administration (50–150 mg) for 14 days, which is consistent with pimavanserin's long plasma half-life (57 hours). The oral bioavailability of pimavanserin is 99.7% [46].

18.6 Luvadaxistat (TAK-831)

Luvadaxistat (also known as TAK-831 and NBI-1065844) is a potent investigational, first-in-class oral selective inhibitor with high binding affinity to DAAO inhibitor and supposedly increases the NMDA activity. It is developed for the management of negative symptoms and cognitive impairment associated with schizophrenia (CIAS) [47].

18.7 Cannabidiol

Cannabidiol (CBD) is a phytocannabinoid that is an important constituent of *Cannabis sativa* and has been postulated to be of pharmacological benefits in schizophrenia. Delta-9-tetrohydrocannabinol (THC) is the main psychoactive ingredient in cannabis having anxiogenic, psychotomimetic, and amnestic effects. CBD has been seen to possess anxiolytic, antipsychotic, and anticonvulsant properties. Several trials are underway to establish its therapeutic potential [48].

18.8 Brexpiprazole

Brexpiprazole has been approved by the FDA for treatment of schizophrenia in adults. Its indication was expanded to the treatment of agitation and dementia associated with Alzheimer's disease. It has a high affinity for the D2 and the 5-HT2A receptors and is a potent partial agonist at the 5-HT1A and 5-HT2C receptors. Brexpiprazole has been found to be efficacious for long-term management of schizophrenia as it shows a relatively favorable adverse effect profile besides reducing both positive and negative symptoms and has low tendencies to cause EPS [49].

18.9 Samidorphan and olanzapine

Samidorphan, a μ-opioid receptor antagonist, and olanzapine combination marketed as Lybalvi, is used in the treatment of adults with schizophrenia and bipolar disorder 1. The combination is available as an oral tablet composed of multiple strengths of olanzapine (5–20 mg) and a fixed dose of 10 mg of samidorphan. In studies enrolling healthy adults and adults with schizophrenia, the combination of olanzapine with samidorphan, a μ-opioid receptor antagonist, mitigated weight gain associated with olanzapine monotherapy [50].

18.10 Sarcosine

N-methyl-glycine (sarcosine) is a potent inhibitor of glycine transporter-1. Sarcosine generally has negligible side effects and is very well tolerated by people with schizophrenia. Larger and longer studies with adequate sample sizes are mandated to better estimate the long term effectiveness and safety and to establish the therapeutic potential of sarcosine as an augmentation therapy to present antipsychotic therapy [51].

18.11 Bitopertine

It is an alternative formulation for schizophrenia that focuses primarily on the disturbances of brain glutamatergic neurotransmission, particularly at the NMDA receptors (NMDAR). Long-term trials are needed to establish its therapeutic benefits [52].

18.12 Repetitive transcranial magnetic stimulation (rTMS)

rTMS is widely used in the treatment of various psychiatric disorders. Stimulation of patients' temporoparietal areas may treat schizophrenic patients' hallucinatory symptoms, and stimulation of patients' frontal areas may improve patients' negative symptoms and cognition. Because of the slow disease progression, patients often have to take the medication for a long time, so the side effects of the medication cannot be ignored. The side effects of long term anti-schizophrenia medication can cause a plethora of side effects including insulin antagonism, adrenaline antagonism affecting glucose and lipid metabolism, cardiac arrhythmias, and other various adverse reactions. Although several trials are underway, large-scale studies are needed to establish their therapeutic benefits [53].

19. Conclusion

Schizophrenia is a serious mental disorder that affects the patients and their relatives. The management of schizophrenia involves an interplay of both the pharmacological and non-pharmacological interventions. A total of ≥30% of patients remain resistant to the existing treatment. Newer drugs targeting various targets are in different phases of drug development. The quest for an optimally designed drug with desirable safety and efficacy is still on.

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