

Research Article

Psychopharmacological treatment of Schizophrenia - An overview of recent research

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ABSTRACT

Schizophrenia and other schizophrenia-spectrum disorders are neurodevelopmental disorders which may share genetic susceptibility factors and represent differential expressions of an underlying vulnerability. Schizophrenia may have its onset in childhood and can be reliably diagnosed. Although the prevalence of schizophrenia in childhood is low, children who develop schizophrenia in adult life may show subtle and non-specific developmental abnormalities, consistent with the neurodevelopmental hypothesis. Further advances in our knowledge of the aetiopathology of schizophrenia may further improve our ability to predict disease development, making implementation of preventive interventions more achievable. The introduction of second-generation antipsychotics and cognitive therapies for schizophrenia over the past two decades generated considerable optimism about possibilities for recovery. We trace the evolution of various treatments for schizophrenia and summarize current knowledge about available pharmacological and psychosocial treatments. Examines the issues around conventional schizophrenia treatment including the problems with side effects and noncompliance, the introduction of newer atypical neuroleptics and their potential for improvement, and issues around pharmaceutical research and public pressures to get new medications approved. In this article, the specificity and characterization of schizophrenia, drug therapy. and the development and future prospects of neuroleptic drugs are reviewed.

Keywords: Schizophrenia, causes, Atypical antipsychotics, Conventional antipsychotics.

INTRODUCTION

Schizophrenia usually first appears in a person during their late teens or throughout their twenties. It affects more men than women, and is considered a life-long condition which rarely is "cured," but rather treated. The primary treatment for schizophrenia and similar thought disorders is medication. Unfortunately, compliance with a medication regimen is often one of the largest problems associated with the ongoing treatment of schizophrenia. Because people who live with this disorder often go off of their medication during periods throughout their lives, the repercussions of this loss of treatment are acutely felt not only by the individual, but by their family and friends as well.

Successful treatment of schizophrenia, therefore, depends upon a life-long regimen of both drug and psychosocial, support therapies. While the medication helps control the psychosis associated

with schizophrenia, it cannot help the person find a job, learn to be effective in social relationships, increase the individual's coping skills, and help them learn to communicate and work well with others. Poverty, homelessness, and unemployment are often associated with this disorder, but they don't have to be. If the individual finds appropriate treatment and sticks with it, a person with schizophrenia can lead a happy and successful life. But the initial recovery from the first symptoms of schizophrenia can be an extremely lonely experience. Individuals coping with the onset of schizophrenia for the first time in their lives require all the support that their families, friends, and communities can provide. A sudden stopping of treatment will most often lead to a relapse of the symptoms associated with schizophrenia and then a gradual recovery as treatment is reinstated.¹

The introduction of second-generation antipsychotics and cognitive therapies for schizophrenia over the past two decades generated considerable optimism about possibilities for recovery. In view of our improved understanding of the etiology and pathophysiology of schizophrenia, there is an opportunity to develop prevention strategies and treatments based on this enhanced knowledge.²

Schizophrenia

Schizophrenia, also sometimes called split personality disorder, is a chronic, severe, debilitating mental illness that affects about 1% of the population, corresponding to more than 2 million people in the United States alone. It affects men about one and a half times more commonly than women. It is one of the psychotic mental disorders and is characterized by symptoms of thought, behavior, and social problems. The thought problems associated with schizophrenia are described as psychosis, in that the person's thinking is completely out of touch with reality at times. The individual with this disorder may also have disorganized speech, disorganized behavior, physically rigid or lax behavior (catatonia), significantly decreased behaviors or feelings, as well as delusions.³

Schizophrenia symptoms usually develop slowly over months or years. Sometimes people may have many symptoms, and at other times people may only have a few. People with any type of schizophrenia may have difficulty keeping friends and working. They may also have problems with anxiety, depression, and suicidal thoughts or behaviors. Symptoms can vary, depending on the type of schizophrenia.⁴

History of Schizophrenia

The term schizophrenia has only been in use since 1911. Soon before that, it was deemed a separate mental illness in 1887 by Emil Kraepelin. Despite that relatively recent history, it has been described throughout written history. Ancient Egyptian, Hindu, Chinese, Greek, and

Roman writings described symptoms similar to the positive symptoms of schizophrenia. During medieval times, schizophrenia, like other illnesses, was often viewed as evidence of the sufferer being possessed by spirits or evil powers.

Types of Schizophrenia

There are five types of schizophrenia, each based on the kind of symptoms the person has at the time of assessment:⁶

- **Paranoid schizophrenia:** The individual is preoccupied with one or more delusions or many auditory hallucinations but does not have symptoms of disorganized schizophrenia.

- **Disorganized schizophrenia:** Prominent symptoms are disorganized speech and behavior, as well as flat or inappropriate affect. The person does not have enough symptoms to be characterized as catatonic schizophrenic.

- **Catatonic schizophrenia:** The person with this type of schizophrenia primarily has at least two of the following symptoms: difficulty moving, resistance to moving, excessive movement, abnormal movements, and/or repeating what others say or do.

- **Undifferentiated schizophrenia:** This is characterized by episodes of two or more of the following symptoms: delusions, hallucinations, disorganized speech or behavior, catatonic behavior or negative symptoms, but the individual does not qualify for a diagnosis of paranoid, disorganized, or catatonic type of schizophrenia.

- **Residual schizophrenia:** While the full-blown characteristic positive symptoms of schizophrenia (those that involve an excess of normal behavior, such as delusions, paranoia, or heightened sensitivity) are absent, the sufferer has less severe forms of the disorder or has only negative symptoms (symptoms characterized by a decrease in function, such as withdrawal, disinterest, and not speaking).

Symptoms

Schizophrenia symptoms usually develop slowly over months or years. Sometimes people may have many symptoms, and at other times people may only have a few. People with any type of schizophrenia may have difficulty keeping friends and working. They may also have problems with anxiety, depression, and suicidal thoughts or behaviors.⁷

At first, patients may have the following symptoms

- Irritable or tense feeling
- Difficulty sleeping
- Difficulty concentrating

As the illness continues, problems with thinking, emotions and behavior develop, including:

- Lack of emotion (flat affect)
- Strongly held beliefs that are not based in reality (delusions)
- Hearing or seeing things that are not there (hallucinations)
- Problems paying attention
- Thoughts "jump" between unrelated topics ("loose associations")
- Bizarre behaviors
- Social isolation

Symptoms can vary, depending on the type of schizophrenia.

Causes of Schizophrenia

No single cause can account for schizophrenia. Rather, it appears to be the result of multiple causes such as genetic factors, environmental and psychological assaults, and possible hormonal changes that alter the brain's chemistry.⁸

1. Abnormalities in Brain Structure, Circuitry, and Chemicals

Brain scans using magnetic resonance imaging (MRI) have shown a number of abnormalities in the brain's structure associated with schizophrenia. Such problems can cause nerve damage and disconnections in the pathways that carry brain chemicals. Enlarged brain ventricles are seen in some schizophrenics, indicating a deficit in the volume of brain tissue. There is also evidence of abnormally low activity in the frontal lobe,

the area of the brain responsible for planning, reasoning, and decision-making. *Abnormal Brain Chemicals.* Schizophrenia is associated with an unusual imbalance of neurotransmitters (chemical messengers between nerve cells) and other brain chemicals, such as dopamine overactivity, glutamate, reelin, and others. Whether any changes in these chemicals in the brain is a cause or a consequence of schizophrenia remains unclear.

Abnormal Circuitry. Abnormalities in brain structure are also reflected in the disrupted connections between nerve cells that are observed in schizophrenia. Such miswiring could impair information processing and coordination of mental functions. For example, auditory hallucinations may be due to miswiring in the circuits that govern speech processing. Strong evidence suggests that schizophrenia involves decreased communication between the left and right sides of the brain.

2. Genetic Factors

Schizophrenia undoubtedly has a genetic component. The risk for inheriting schizophrenia is 10% in those who have one immediate family member with the disease and about 40% if the disease affects both parents or an identical twin. Family members of patients also appear to have higher risks for the specific symptoms (negative or positive) of the relative with schizophrenia.

3. Environmental causes of schizophrenia

Several stress-inducing environmental factors that may be involved in schizophrenia, including:

- Prenatal exposure to a viral infection
- Low oxygen levels during birth (from prolonged labor or premature birth)
- Exposure to a virus during infancy
- Early parental loss or separation

HISTORY OF OUR UNDERSTANDING OF SCHIZOPHRENIA TREATMENT

Antipsychotic drugs for the treatment of schizophrenia arrived in the clinic in the fifties of the previous century. Until the

early fifties, the treatment of schizophrenia was very limited and usually confined to either inducing a condition of shock with for instance cardiazol, insulin or electrical current, or cutting the connections between the frontal cortex and the deeper brain regions. The general idea behind the shock treatment was that the brain needed to be re-set.⁹

The synthesis of chlorpromazine (4560RP) in 1950 and its subsequent use in schizophrenic patients by Hamon and Delay and Deniker and their colleagues in 1952, marked the beginning of a revolution in the treatment of schizophrenia¹⁰. Chlorpromazine was the first chemical compound which was able to selectively reduce hallucinations and delusions. Its pharmacologic characteristic of dopamine receptor blockade was linked to its antipsychotic action¹¹. Several different chemical families of neuroleptics were identified, developed, and introduced in the next 2 decades. Additional phenothiazines like fluphenazine, trifluoperazine and thioridazine were introduced onto the market in the 1950s. In addition, especially in Europe the butyrophenone haloperidol and its close analogues, and the thioxanthenes such as thiothixene, flupenthixol and chlorprothixene became equally popular in the treatment of schizophrenia.

This widespread use of antipsychotic drugs led to a rapid decline in the number of inpatients in psychiatric institutions, but, at the same time, also led to the realization that antipsychotics have several important side effect, most notably the extrapyramidal side effects (EPS, parkinsonism, dystonia and akathisia) and in 1961 the prevalence of EPS was estimated at almost 40%¹². In addition, at the end of 1950 antipsychotic induced tardive dyskinesia also reported¹³. After this early productivity, drug discovery almost stopped in the area of schizophrenia therapeutics for about 15 years. After 1978 until the approval of clozapine for psychosis in 1990, no new antipsychotic drugs were brought before the United States (US) Food and Drug Administration (FDA).

The fact that this drug was an effective antipsychotic although devoid of inducing EPS, earned it the title of an "atypical antipsychotic"¹⁴. After report on drug-induced agranulocytosis in Finland, clozapine was withdrawn from the market in 1977¹⁵, only under strict conditions in 1990 after a landmark study showed its superiority over chlorpromazine¹⁶. Its unique clinical profile led to an intensified search for new antipsychotics that, like clozapine, would lack EPS but unlike clozapine, would also lack the risk of agranulocytosis. Thus, after a dry spell in the 1970s and 1980s (with only one or two novel antipsychotics being approved in two decades), the 1990s saw the introduction of risperidone (FDA approval in 1993), olanzapine (1996) and quetiapine (1997), followed by ziprasidone (2001) and aripiprazole (2002). In addition three additional antipsychotics were approved by the FDA in 2009: iloperidone, asenapine and paliperidone palmitate (which is the 9-OH derivative of risperidone) and lurasidone was approved by the FDA in October 2010.

COMMONLY USED ANTIPSYCHOTIC MEDICATIONS

A. First generation antipsychotics (FGAs)¹⁷

I. Phenothiazines

(A) Aliphatic side chain

Chlorpromazine, chlorproethazine, Cyamemazine, levomepromazine, promazine, trifluoperazine.

(B) Piperidine side chain

Mesoridazine, piperacetazine, pipoptiazine, propericiazine, sulforidazine, thioridazine.

(C) Piperazine side chain

Fluphenazine, acetophenazine, butaperazine, dixyrazine, perazine, perphenazine, prochlorperazine, thiopropazate, thioproperazine, trifluoperazine

II. Butyrophenones

Haloperidol, benperidol, blonanserin, bromperidol, droperidol, fluanisone, melperone, moperone, pipamperone, timiperone,

trifluoperidol.

III. Thioxanthenes

Thiothixene, chlorprothixene, clopenthixol, flupenthixol, zuclopenthixol

IV. Dihydroindolones

Molindone, oxypertine

V. Dibenzoxazepines

Loxapine, clotiapine

VI. Diphenylbutylpiperidines

Pimozide, fluspirilene, penfluridol

VII. Benzamides

Sulpiride, nemonapride, sultopride, tiapride

VIII. Iminodibenzyl

Clocapramine, mosapramine

B. Second Generation antipsychotics (SGAs)

I. Benzo (diazep- or thiazep-) pines

Asenapine, Clozapine, Olanzapine, Quetiapine, Zotepine

II. Indolones and diones

Aripiprazole, iloperidone, paliperidone, perospirone, risperidone, sertindole, ziprasidone

III. Benzamide

Amisulpride

Antipsychotic Drug Therapy- Mechanism of Action

All antipsychotic drugs tend to block D₂ receptors in the dopamine pathways of the brain. This means that dopamine released in these pathways has less effect. Excess release of dopamine in the mesolimbic pathway has been linked to psychotic experiences. It is the blockade of dopamine receptors in this pathway that is thought to control psychotic experiences.¹⁸

- Typical antipsychotics are not particularly selective and also block dopamine receptors in the mesocortical pathway, tuberoinfundibular pathway, and the nigrostriatal pathway. Blocking D₂ receptors in these other pathways is thought to produce some of the unwanted side effects that the typical antipsychotics can produce.

- Atypical antipsychotic drugs have a similar blocking effect on D₂ receptors.

Some also block or partially block serotonin receptors (particularly 5HT_{2A}, C and 5HT_{1A} receptors). The additional effects on serotonin receptors may be why some of them can benefit the "negative symptoms" of schizophrenia.²⁰

- Parkinsonism and extrapyramidal effects occur with antipsychotics which have a high affinity for D₂ and which are, therefore, tightly bound to D₂. Clozapine and quetiapine have a low affinity for D₂, and, being readily displaced by endogenous dopamine, do not give rise to extrapyramidal effects. Because the loosely bound antipsychotics dissociate from D₂ more rapidly.

Side Effects of antipsychotics

Antipsychotics are associated with a range of side effects. Extrapyramidal reactions include acute dystonias, akathisia, parkinsonism (rigidity and tremor), tardive dyskinesia, tachycardia, hypotension, impotence, lethargy, seizures, intense dreams or nightmares, and hyperprolactinaemia. In "healthy" individuals without psychosis, doses of antipsychotics can produce the negative symptoms (e.g. emotional and motivational difficulties) associated with schizophrenia.²¹

Following are details of the side effects of antipsychotics:

- Antipsychotics, particularly atypicals, appear to cause diabetes mellitus and fatal diabetic ketoacidosis.²²
- Antipsychotics may cause pancreatitis.²³
- The atypical antipsychotics (especially olanzapine and clozapine) seem to (due to occupancy of the histamine receptor) cause weight gain more commonly than the typical antipsychotics.²⁴
- Antipsychotics increase the likelihood of a fatal heart attack, with the risk of death increasing with dose and the length of time on the drug.²⁵
- Clozapine also has a risk of inducing agranulocytosis, a potentially dangerous reduction in the number of white blood cells in the body. Because of this risk,

patients prescribed clozapine may need to have regular blood checks to catch the condition early if it does occur, so the patient is in no danger.²⁶

- One of the more serious of these side effects is tardive dyskinesia, in which the sufferer may show repetitive, involuntary, purposeless movements.

- A potentially serious side effect of many antipsychotics is that they tend to lower an individual's seizure threshold. Chlorpromazine and clozapine, in particular, have a relatively high seizurogenic potential.

- Dysphoria.

- Drug-induced parkinsonism due to dopamine D2 receptor blockade may mimic idiopathic parkinsonism.

- Sexual dysfunction, which may rarely continue after withdrawal, similar to Post-SSRI sexual dysfunction (PSSD).

- Hyperprolactinaemia. The breasts may enlarge and discharge milk, in both men and women due to abnormally-high levels of prolactin in the blood. Prolactin secretion in the pituitary is normally suppressed by dopamine. Drugs that block the effects of dopamine at the pituitary or deplete dopamine stores in the brain may cause the pituitary to secrete prolactin.²⁷

There is a possibility that the risk of tardive dyskinesia can be reduced by combining the anti-psychotics with diphenhydramine or benztropine, although this remains to be established. Central nervous system damage is also associated with irreversible tardive akathisia and/or tardive dysphrenia.

ATYPICAL ANTIPSYCHOTICS

The second-generation antipsychotics, also commonly known as atypical antipsychotics, are among the most significant medicines developed in the past decade for the treatment of mental disorders such as schizophrenia, schizoaffective disorder, and mania. These agents are atypical because they are significantly different, both in structure and pharmacology, from the older, typical antipsychotic medications. Having multiple

mechanisms of action in the brain, the second-generation antipsychotics have wider applications than just for the treatment the "positive" symptoms of psychosis (e.g., hallucinations, delusions, bizarre behavior, disorganized speech).

These medicines have proven to be highly effective for treating negative symptoms of schizophrenia, which are characterized by emotional and social withdrawal, flat affect, lack of spontaneity, inability to feel pleasure, attention impairment, and other restrictions in thought, speech, and behavior. Thus most clinicians view second-generation antipsychotics not merely as antipsychotic medications but also as psychotropic agents, which are effective in treating a wide spectrum of mental disorders.

In addition to blocking the dopamine D2 receptor, most antipsychotics, and especially the SGAs also inhibit a large number of other receptors, including other dopaminergic (D1, D3 or D4), serotonergic (especially 5-HT_{2A} and 5-HT_{2C}), adrenergic (mainly α_1) and histaminergic (especially H₁). Most of these receptors have been linked to side effects like weight gain (5-HT_{2C} and H₁), drowsiness (H₁), sexual dysfunction (5-HT₂) and orthostatic hypotension (α_1). On the other hand, it has also been hypothesized that the 5-HT_{2A} receptor blockade might be beneficial with respect to the negative and/or cognitive symptoms of schizophrenia as well as to a reduced risk for EPS.²⁸

Comparative effectiveness of antipsychotics in the treatment of Schizophrenia

The broad objectives of treatment are to reduce the mortality and morbidity of the disorder by decreasing the frequency and severity of episodes of psychotic exacerbation and improving the functional capacity and quality of lives of the individuals afflicted with the illness.

In the past decade, second-generation antipsychotics have essentially replaced the older, conventional antipsychotics. The primary reason for this is that the second-generation antipsychotics are

much better tolerated than their older counterparts. The second-generation agents are associated with a substantially lower risk of EPS and tardive dyskinesia (TD). EPS are acute-onset movement disorders characterized by muscular rigidity, tremors, shuffling movement, restlessness, and muscle spasms resulting in abnormal posture. TD is a delayed-onset condition that consists of abnormal involuntary movements usually involving the tongue and mouth and sometimes the arms and trunk. EPS and TD are substantial risks with conventional antipsychotics. Patients frequently cannot, and will not, tolerate the side effects of antipsychotics, and this becomes problematic if long-term treatment is needed. With their more favorable side effect profile, the newer antipsychotics are better tolerated, and patients are more likely to take them consistently.²⁹

The other distinguishing advantage of the second-generation antipsychotics is that they are superior in treating negative symptoms. In areas of the brain where emotion and cognition are affected by the balance of serotonin and dopamine, the dual action of the second-generation agents resets this important balance when it has been altered. In patients with mental disorders such as schizophrenia, the balance of these neurotransmitters is disturbed, and patients may manifest negative symptoms.

Clozapine, the first so-called atypical or subsequently labeled "second-generation" antipsychotic (SGA), was introduced into clinical practice in the late 1960s. It does not cause EPS or tardive dyskinesia. Its other adverse effects, however, have substantially limited its utilization and agranulocytosis kept it out of most parts of the world until the 1990s. The fact that it was found to be more effective than FGAs in treatment-refractory patients and in reducing suicidality,³⁰ and was devoid of significant short-term and long-term motor side-effects led to optimism that better antipsychotic treatments for schizophrenia were possible.

Other pharmacological targets

All current antipsychotic therapies have been developed on the half-century old platform of dopamine D2 receptor antagonism. The potent serotonin 5HT-2A antagonism characteristic of the more recently developed so-called second generation antipsychotic agents is associated with a lower risk of neuromotor side-effects (EPS and tardive dyskinesia). In view of the therapeutic limitations of these approaches, a range of other molecular and cellular strategies are being evaluated in schizophrenia. In addition to other dopamine and serotonin receptors, a variety of glutamatergic, cholinergic, gabaergic, neuropeptidic, cannabinoid, and nonneurotransmitter receptor targets are also being studied in the treatment of schizophrenia.³¹

Psychotherapies and social treatments

Although antipsychotic medications are the mainstay of treatment for schizophrenia, pharmacotherapy alone produces only limited improvement in negative symptoms, cognitive function, social functioning and quality of life. Additionally, many patients continue to suffer from persistent positive symptoms and relapses particularly when they fail to adhere to prescribed medications. This underlines the need for multi-modal care including psychosocial therapies as adjuncts to antipsychotic medications to help alleviate symptoms and to improve adherence, social functioning and quality of life³². We briefly review evidence that has accumulated on the efficacy of the major modalities of psychosocial treatment.

Importance of extended release delivery systems to antipsychotics

Antipsychotic drugs have revolutionised the therapy and management of schizophrenia. However, patient compliance rates are very poor due to the nature of the disease and troublesome side-effects, and are major causes of symptom recurrence. Although some new antipsychotic agents have been marketed to offer broader efficacy with much reduced side-effect profiles, the drug

delivery systems for antipsychotics are still in the stage of conventional dosage forms, such as tablets, capsules and solutions, and need to be dosed at the frequency of 2-4 times daily. Doubtless, novel drug delivery systems, such as sustained and controlled release systems, will be useful for antipsychotics. They should reduce the frequency of dosing, enhance drug bioavailability and improve patient compliance.¹⁹

CONCLUSION

To conclude, the pharmacological treatment of schizophrenia has improved markedly since the introduction of oral conventional antipsychotic drugs. Second-generation 'atypical' antipsychotics then combined efficacy that is as good as that of conventional agents with improved safety and tolerability. Most recently, the first long-acting, injectable formulation of a second-generation antipsychotic has been developed. These formulations should optimize efficacy, tolerability and compliance among patients with chronic schizophrenia who require long-term therapy and have the potential to become the standard treatment in this group of individuals. There is now new research going into the treatment of schizophrenia. The inevitable result of that is that, whether with the current class of atypical neuroleptics, newer medications, or other treatment modalities, there will eventually be a safe and effective way of dealing with schizophrenia.

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