Pharmacotherapy of schizophrenia

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Traditionally, schizophrenia was considered to be a severe psychiatric disorder, with a chronic course and an unfavorable outcome. Throughout history, there has been incidence of schizophrenia, roughly one percent of the population, consistently, in every culture. It is generally acknowledged that schizophrenia has multifactorial etiology, with multiple susceptibility genes interacting with environmental insults to yield a range of phenotypes in the schizophrenia spectrum. The discovery of antipsychotics in the 1950s revolutionized the treatment of schizophrenia and focused on the positive symptoms. By the 1960s, however, it became evident that the reduction in positive symptoms did not lead to recovery from schizophrenia and did not significantly improve the functional outcome. The advent of the novel antipsychotics during the last 15 years represents a significant improvement over the effectiveness of conventional antipsychotics. These agents are, however, not a magic bullet and bear their own side effects, such as weight gain, diabetes, hyperprolactinemia, and QTc prolongation. Nevertheless, at this point, they seem to be more effective and safer than the conventional antipsychotics. Moreover, advances in the treatment of schizophrenia have been and continue to be urgently needed.
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Schizophrenia is a devastating neurobiologic disorder that typically strikes the brain function of adolescents and young adults, occulting in about 1 of every 100 people worldwide. The direct costs of schizophrenia account for 2.5% of US health expenditures. Despite these expenditures, up to half of all people with schizophrenia at any point in time are not receiving active psychiatric care, and at least 15% to 20% of people suffering from the disorder will never receive any psychiatric treatment. Moreover, although the financial costs of schizophrenia can be calculated, the cost of unrealized human potential and lost dignity associated with the disease are beyond computation. For all of these reasons, advances in the treatment of schizophrenia have been and continue to be urgently needed (1-7).

What is schizophrenia?
Criteria for diagnosis of schizophrenia, defined by the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) (8), dictate that at some stage of the illness, patients experience at least two of five types of characteristic symptoms. The four positive symptoms - so called because they indicate the product of an abnormal disease process - include delusions, hallucinations, grossly disorganized or catatonic behavior and disorganized speech, and are considered to be psychotic since they are inconsistent with the experiences of normal humans. Symptoms such as withdrawal, anhedonia, anergia and affective flattening, are termed negative because they indicate a deficit of normal function and are not psychotic (Table 1). However, the onset, time course and nature of the disturbances in emotion, personality, cognition and motor activity exhibited by patients with schizophrenia vary widely (9, 10).

Background and historical perspective
The first consideration of pharmacotherapy for schizophrenia came with the use of Rauwolfia alkaloids, first considered in 1931, and gained considerable interest by the early 1950s. Toxic substances, e.g., insulin and metrazol were used to induce shock treatments. Prior to the inception of modern pharmacotherapy, i.e., tranquillisers, there was experimentation with hashish and cocaine (7). LSD was synthesized in 1943. Its psychedelic effects were later used for recreational purposes, as well as for investigating the human psyche. Some psychotherapeutic benefit was proposed from LSD (6). These esearches, although highly restricted, continues. LSD came into disrepute when it was proposed as a chemical warfare agent, and when it was used by the US intelligence community in efforts to brain-wash individuals through a technique called "Psychic Driving". Psychic driving was tested on

unsuspecting hospitalized mentally ill people without their consent (7).

Table 1. Clinical Features of schizophrenia

Positive symptoms (function distorted) Hallucinations (perception) Delusions (inferential thinking) Disorganized speech Bizarre behavior	These are essentially disordered versions of the normal brain functions of thinking, perceiving, formation of ideas and sense of self. Patients with thought disorder may present with complaints of poor concentration or of their mind being blocked or emptied: a patient stopping in a perplexed fashion while in mid-speech and the interviewer having difficulty in following the speech are typical signs
Negative symptoms (functions diminished) Alogia (fluency of speech/thought) Affective blunting (emotional expression) Avolition (volition and drive) Anhedonia/asociality (ability to feel pleasure, experience emotional attachments, and/or form relationships with others) Attention impairment (focusing attention)	These involve loss of personal abilities such as initiative, interest in others and anhedonia. Blunted or fatuous emotions (flat affect) limited speech and prolonged periods of inactivity are typical behaviors.

From the introduction of conventional antipsychotics that sparked massive deinstitutionalization in the 1960s to the reintroduction of clozapine in 1988 and the discovery of atypical antipsychotics, the struggle to effectively treat schizophrenia and related disorders continues. The introduction of chlorpromazine (CPZ) in 1952 was an indisputable advance in psychiatry. CPZ's efficacy in treating the positive symptoms of schizophrenia is well established. Over the next 20 years, about 40 similar medications were introduced world-wide into the market, comprising a class of antipsychotic medications now termed "typicals". All typicals studied have similar mechanisms of action and comparable efficacy. The choice of medication among the typicals thus is largely based on their relative side effect profile (4, 7). The two most troublesome side effects are extrapyramidal side effects (EPSEs) and tardive dyskinesia. (TD). The debilitating symptoms of EPSEs are now known to occur in 75% to 90% of patients taking typicals. The annual cumulative incidence of TD in young, healthy adults taking typicals is 4% to 5%, and the risk increases with age and duration of exposure to the medication. Further, cases of TD were recognized as being disfiguring, irreversible, and potentially fatal as early as the late 1960s (7). Moreover, studies began to emerge suggesting that much of the functional disability associated with schizophrenia is associated with negative symptoms and cognitive deficits, for which the typicals showed little potential treatment efficacy (7). After a hiatus of almost 15 years, clozapine was reintroduced in North America following the landmark trial by Kane and others in 1988 comparing clozapine with CPZ in treatment-refractory schizophrenia. It was the first antipsychotic shown to be more effective then haloperidol and CPZ for positive symptoms and, incidentally, negative symptoms. It also offered a better side effect profile free of EPSEs and TD. With its unique pharmacology and relatively low D2 antagonism and more potent 5-HT2 antagonism, clozapine became the prototype atypical antipsychotic. The confirmation of clozapine's superior efficacy in treating patients with schizophrenia compared with the typical antipsychotics, triggered further pharmaceutical industry research for more similarly effective newer medications (4, 7).

Etiology of schizophrenia

It is unclear whether schizophrenia is an old or modern illness. Ancient records (first century) describe a type of insanity in persons labeled either "gifted" or "cursed" depending on religious criteria, and early treatment often involved care by the family or church, but some early hypotheses considered the possibility that brain damage or malformation could account for these behaviors. Some authorities argue that no descriptions of true schizophrenia were published until more modern times. The term schizophrenia (splitting of the mind) was introduced in 1911 and is meant to convey a splitting of usually integrated psychic functions (4, 11-13).

The onset of symptoms differentiable from non affected twins tends to cluster around certain ages (0–5 and 13–17 y), with a predominance of boys in the younger range and equal number of males and females in the older age group (7).

There is no clear difference in occurrence of schizophrenia among different cultures. Some computed tomography and magnetic resonance imaging studies suggest possible increased cerebral ventricular size, decreased brain mass, or decreased left temporal lobe size in certain subsets of patients with schizophrenia. Some neurodevelopmental models implicate possible abnormal brain circuitry maturation during the second trimester of gestation. Enviromental factors such as viruses, pollution, trauma, dietary deficiencies, toxins, infections, or insecticides have all been invoked as causative. Most experts, however, believe that schizophrenia results from a complicated interplay of environmental, biologic, psychological, cultural, and genetic factors (4, 11-13).

Biochemical basis

In the past 20 years, findings in several basic researches have provided hypotheses about pathophysiology of schizophrenia. This research, which spans many different disciplines, includes studies of the receptor pharmacology of neuroleptics at dopamine, serotonin,

glutamate, purinergic and muscarinic receptors, electrophysiological studies with rats treated chronically with drugs, and molecular biological studies measuring the expression of immediate early genes (14-20).

Dopamine hypothesis

Scientists have noted the role of dopamine in schizophrenia since they uncovered the chemical reactions behind the early antipsychotics (21).

However, the exact nature of its role has long been - and remains - in dispute. The first model of the role of dopamine in schizophrenia was the dopamine hyperactivity hypothesis. This asserts that hyperactivity of the brain's dopaminergic systems is directly responsible for the symptoms of schizophrenia (22-24). In the period since its inception, this hypothesis has been accepted, studied and supported by neuroscientists. One supportive observation involves the actions of drugs that enhance the activity of dopaminergic systems. Amphetamine is one such drug; when used chronically for a long time, amphetamines can induce symptoms virtually identical to those of a paranoid psychosis.

The dopamine hypothesis was the first durable biological framework for understanding the etiology and treatment of schizophrenia (21, 22); however, it failed to explain many aspects of schizophrenia, such as negative symptoms, cognitive deficits and other neurochemical and pathological findings (Table 1).

Interest in dopamine interactions with other neurotransmitter systems has contributed to the development of novel antipsychotics with better clinical efficacy (21, 22-24).

In addition, another weakness of the dopamine hypothesis involves the time course of the clinical effects of antipsychotics. While neuroleptics block D2 receptors shortly after crossing the blood-brain barrier, their antipsychotic effects do not reach a clinically significant level until, on average, one to two weeks later.

In addition, antipsychotics neither cure the illness, nor stop the relapse of symptoms completely, and about 30% of patients are refractory to treatment with dopamine blockers. In this regard, the atypical antipsychotics, which are less specific blockers of dopamine, may be superior to haloperidol and result in fewer extrapyramidal symptoms (21, 22). The major limitations of conventional antipsychotic drugs are their marked tendency to cause extrapyramidal symptoms, poor efficacy against negative schizophrenic symptoms, inability to reverse or prevent the development of the cognitive impairment of schizophrenia and inability to permit a normal level of psychosexual and work or function. These factors lead to a poor quality of life even for patients whose positive and disorganized symptoms respond to neuroleptic treatments (14-19).

Serotonin hypothesis

Serotonin (5-HT) is an essential neurotransmitter synthesized from dietary tryptophan. A possible role of 5HT in schizophrenia was first recognized in the 1950s when researchers noticed its similarity to lysergic acid diethylamide (LSD) (25). LSD competes for and occupies 5HT receptor sites with very high potency, resulting in psychosis-like symptoms. These observations eventually led to a hyper-serotonin hypothesis for schizophrenia. Like dopamine, evidence for the actions of 5-HT in schizophrenia lies in observations of brain-behavior relations, neurotransmitter systems, drug mechanisms and postmortem studies. Some studies have found elevated 5HT levels in blood platelets. These studies indicate that CSF levels of both 5-HT and its primary metabolite 5hydroxyindolacetic acid are more reflective of brain 5-HT transmission (26, 27). However, reports of CSF levels are quite conflicting. The strongest evidence of the role of 5-HT in schizophrenia, by far, is the mechanism of atypical antipsychotic drugs like clozapine. These drugs, which have provided dramatic improvements in patients that were resistant to other medications, interestingly, show a weak direct dopaminergic antagonist effect. They are also very selective of where and on which receptors they act. One could conclude, therefore, that the principal mechanism of symptom relief with atypical antipsychotics is from something other than dopamine antagonism (28-31). This mechanism is probably 5-HT antagonism. This hypothesis was supported when researchers combined typical antipsychotics with a 5-HT2 antagonist like ritanserin (28-31).

When used in combination they resulted in substantial relief of patients' negative symptoms and motoric side effects. The theory of a 5-HT-dopamine interaction as the mechanism behind schizophrenia is beginning to gain wide acceptance. However, the exact role of 5-HT is still not clear. Its effects on dopamine aside, 5-HT has a great deal of direct inhibitory effect on prefrontal neurons. One cannot ignore the possible role of such actions on schizophrenia and further investigation is warranted (32, 33).

Other receptors

Line of evidence has been accumulating that implicates the involvement of cholecystokinin, neurotensin, gluta-mate, α2-adrenoceptor, and other receptor systems in the pathophysiolohy of schizophrenia. For example, the corticostriatal glutamate pathway may directly or indirectly (via γ-aminobutyric acid (GABA)) inhibit dopamine function from the ventral striatum leading to increased inhibitory activity in the limbic system. Therefore, decreased activation of glutamate receptors may increase limbic dopamine release, producing symptoms that parallel the apparent limbic dopaminergic hyperactivity thought to be associated with the positive

symptoms of schizophrenia. Adenosine receptors have also been implicated (7).

Studies of the four recently cloned adenosine receptors (A1, A2A, A2B, A3) propose that the A2A receptor may have the ability to interact with other neurotransmitter receptors, including the dopamine D2 receptor. In animal models, the A2A agonist CG21680 (2-(4-(2-carboxyethyl)-phenethylamino) adenosine-5′-*N*-ethyluronamide) appears to have antipsychotic efficacy and, conversely, the adenosine competitive antagonist, caffeine, potentiates behavioral effects similar to a dopamine agonist. A modulation of dopamine D2 receptors by adenosine A2 receptors in the ventral striatum has been proposed and supported by few clinical trials (7, 20).

Pharmacotherapy of schizophrenia

The 1990s could justifiably be seen as the decade of psychopharmacology. Since 1990, five new antipsychotics have been approved for use in the USA: risperidone, olanzapine, sertindole (subsequently withdrawn), quetiapine and ziprasidone. These antipsychotics, along with the protypical drug clozapine, are all considered atypical (32-36).

Why atypical antipsychotics?

The outcome for many schizophrenic patients treated with conventional antipsychotics is unsatisfactory. Most controlled trials continue to find a subgroup of 10 to 20% of patients who derive little benefit from typical antipsychotic therapy (7). Moreover, there is 20 to 30% relapse during the first two years of drug treatment in patients who were initially responsive to antipsychotic drugs (7). Classical antipsychotic drug treatment appears to have little effect on either the chronic course of the illness or negative symptoms. The negative symptoms tend to be persistent, disabling, difficult to treat and prognostically unfavorable (37-40). The adverse effects associated with conventional antipsychotics, in particular extrapyramidal adverse effects, can result in poor compliance (37, 38).

The treatment of schizophrenia

Modern treatment for schizophrenia relies primarily on somatic drug therapy. Pharmacological treatment for schizophrenia did not begin until approximately a century ago (14, 16). Before this, beliefs surrounding all mental illnesses were grounded in religious dogma and it was not until the 19th century that any substantial advances were made. Drugs from the phenothiazine class were originally used as antihelminthics in veterinary medicine, but in 1950 in Paris, Paul Charpentier synthesized chlorpromazine, a mild antihistamine that appeared notable as a sedative agent and revolutionized psychiatric treatment. In 1952, Jean Delay and Pierre Deniker reported that chlorpromazine was effective in treating patients with acute psychosis (18, 20) while in 1954 in Montreal, Heinz Lehmann reported the successful use of the drug in the treatment of schizophrenia. Chlorpromazine, which is still widely used today, was administered for the next 14 years despite there being little understanding of how or why it worked. Currently two categories of antipsychotics are in common use: typical and atypical antipsychotics (16, 37-39). The former class, which represents the first antipsychotics to reach mainstream use, act primarily on the brain's dopaminergic pathways and show very little regional specificity. Typical antipsychotics are usually effective in controlling the positive symptoms of the illness but are associated with potential complications like neuroleptic malignant syndrome or extrapyramidal side effects and the long-term problem of tardive dyskinesia. Today they are still in common use, but over last few years their dominant position in the treatment of schizophrenia has diminished, as newer, atypical antipsychotic drugs have been developed (14, 16, 37-39). One of the most common and most potent typical antipsychotics in current use is haloperidol, which is thought to work by blocking dopaminergic neurotransmission in the mesolimbic tract. Dopaminergic pathways in this area are thought to be involved in arousal, memory, stimulus processing, locomotor activity and motivational behavior (40, 41). Hyperactivity in the mesolimbic tract causes overexcitation of different processes and is associated with the positive symptoms of schizophrenia (4). Haloperidol, along with other typical antipsychotics is unfortunately not very selective in which dopaminergic pathways it antagonizes (40, 41). This can lead to unwanted reactions in the mesocortical tract and nigrostriatal pathways. The mesocortical tract projects into the prefrontal and frontal cortices (42). This system has been implicated in cognition, communication and social activity impairment. Diminished dopamine activity has been observed in numerous schizophrenia studies and it is thought to be responsible for degradation in the mesocortical's activities (5). As a result, reduced levels of dopamine are believed to be the primary cause of the negative symptoms of schizophrenia. For these reasons, haloperidol, which reduces dopamine levels even further, is relatively ineffective in relieving negative symptoms and at high doses can even lead to exacerbation of these symptoms (43, 44). The newest categories of medications used in the treatment of schizophrenia are the dopamine receptor antagonists (typical antipsychotics) and the serotonin-dopamine antagonists (SDAs) (also called newer, novel, or atypical antipsychotics). Diferentiating the two classes of antipsychotics -dopamine receptor antagonists and SDAs- is increasingly important, since they have different mechanisms of action and different clinical effects (45-48). Clozapine is a heterotricyclic benzodiazepine derivative (34), which was one of the first antipsychotics to demonstrate only limited

extrapyramidal side effects. Its D_1 and D_2 receptor antagonism affinities are low (37, 38) and unlike typical antipsychotics, clozapine has a regional specificity for mesolimbic dopamine tracts, with only weak affinities for striatal D_2 receptors. This regional specificity allows clozapine, and other atypical antipsychotics, to act upon the mesolimbic-induced positive symptoms without creating major side effects. The drug does not block behaviors induced by amphetamine or apomorphine, further suggesting that any dopamine antagonism is secondary to other activities.

The antipsychotic effects of clozapine seem to result in the lessening of both positive and negative symptoms (mainly secondary negative symptoms), without the system-degenerating side effects. It appears to have an acute, clearly dose-dependent effect on the aggressive behavior associated with schizophrenia (49-51). However, even clozapine has unwanted side effects, which necessitate discontinuation of clozapine therapy in about 8% of patients. The most serious side effect, agranulocytosis, is characterized by an abnormally low granulocyte or total white blood cell count (52). Although clozapine has proven extremely successful as an antipsychotic, it cannot be employed to treat schizophrenia until two antipsychotics have failed to produce significant results (53). This fact is almost directly due to the risk of agranulocytosis (53, 54).

Risperidone is the second atypical antipsychotic to come into common use. Unlike clozapine it can be used as a first line therapy against schizophrenia and is in widespread use now. It acts upon the same receptor sites as clozapine with some extra affinities for benzodiazepine receptors, 5-HT$_1$ receptors, α_2-adrenergic and β-adrenergic receptors (36-38) and appears to reduce both positive and negative symptoms with the same efficacy.

The side effect profile of the drug is similar to clozapine, but the risk of extrapyramidal adverse effects appears to be higher and no case of agranulocytosis has ever been documented. Its more frequent prescription rate appears to be due to this lessened side effect risk and its lower cost (36-38).

Olanzapine is the third FDA approved atypical anti-psychotic. Its efficacy seems to match clozapine and risperidone, while the side effect profile is identical to risperidone. Olanzapine specifically blocks 5-HT and D2 receptors and additionally blocks muscarinic (M_1), H_1, 5-HT$_{2c}$, 5-HT$_3$, 5-HT$_6$, α_1, D_1 and D_4 receptors. Its 5-HT blockade is about 8-fold stronger than its dopamine receptor blockade (36-38).

Somnolence, dry mouth, dizziness, constipation, dyspepsia, increased appetite, and tremor are associated with olanzapine use. Olanzapine is somewhat more likely than risperidone to cause weight gain. Two percent of

patients may need a discontinuation of the drug because of transaminase elevation (36-38).

Amisulpride is a selective dopamine D2/D3 receptor blocker. The evaluation of this atypical antipsychotic specifically addressed the question of efficacy in negative symptoms (46). Although amisulpride is not a serotonin-dopamine antagonist, it is not associated with extrapyramidal symptoms. Its exact mechanism of low EPS is not clear but is hypothesized to be a preference for mesolimbic over nigrostriatal dopamine receptors in the animal models (46).

Ziprasidone is an antagoinst of 5-HT1D, 5-HT2A, and 5-HT2C; D2, D3 and a1 receptors. Ziprasidone also has agonist activity at serotonin 5-HT1A receptors and is a serotonin reuptake inhibitor and a norepinephrine reuptake inhibitor. The most common adverse effects in patients taking ziprasidone were somnolence, headache, dizziness, nausea and QT prolongation in those with a history of cardiac arrhythmia (46).

Quetiapine is an antagonist of 5-HT2 and 5-HT6, D1 and D2, H1 and α1 and α2 receptors. It dose not block muscarinic or benzodiazepine receptors. Quetiapine, like clozapine, is not associated with extrapyramidal symptoms. The most common adverse effects of quetiapine are somnolence, postural hypotension and dizziness (55, 56).

Aripiprazole is the newest atypical antipsychotic to come into practice. It is a unique antipsychotic that exhibits partial agonism at the dopamine D_2 and serotonin 5HT$_{1A}$ receptors and antagonism at the serotonin 5HT$_{2A}$ receptors. Aripiprazole also displays a high affinity for dopamine D_2 and D_3, serotonin 5HT$_{1A}$ and 5HT$_{2A}$ receptors, moderate affinity for dopamine D_4, serotonin 5HT$_{2C}$ and 5HT$_7$, α_1 adrenergic and histamine H_1 receptors, and moderate affinity for the serotonin reuptake site. Aripiprazole lacks affinity for the cholinergic muscarinic receptors (57, 58). Aripiprazole is contraindicated in patients with a known hypersensitivity to the product. The risk of neuroleptic malignant syndrome is limited, but still present, with aripiprazole administration. It may be associated with orthostatic hypotension and should be used with caution among patients with cardiovascular or cerebrovascular disease or conditions that predispose patients to hypotension (57, 58). Aripiprazole should be used with caution among patients with a history of seizures or with conditions that lower the seizure threshold. The risk of seizures in preliminary, short term, placebo controlled studies is very low to absent (1/926 or 0.1%) (57, 58).

The safety and efficacy of aripiprazole has not been established among pregnant or breastfeeding women and should be used only if the potential benefits outweigh the risks associated with its use. In addition, the safety and efficacy of aripiprazole has not been established among pediatric and adolescent patients (57, 58).

The incidence of EPS was the same for the aripiprazole and placebo groups at 6%. There were no significant changes in routine serum chemistry, hematology, electrocardiogram or urine analysis measures. There was a slight difference in the mean weight gain between aripiprazole and placebo groups (57, 58).

Emerging adverse effects of the atypicals

In reviewing researches done on the atypical antipsychotics over the last 10 years, long-term side effects of these medications are emerging. Reports about endocrine and metabolic side effects such as hyperprolactinemia, weight gain, obesity, dyslipidemias, diabetes, and cardiac adverse effects are becoming a serious cause for concern (59-62).

Dyslipidemia
Concerns about hypertriglyceridemia and antipsychotic use were raised first in 1995. Clozapine has been linked to an increased risk of hypertriglyceridemia and dyslipidemias (59-61). Among 82 patients in a 5-year naturalistic study, those treated with clozapine for 1 year gained more than 40% of their body weight and had significantly increased serum triglycerides during the 60-month trial period (59-61). Other reports have documented a mean increase in fasting serum tri-glycerides of 60 to 70 mg/dL associated with both short- and long-term olanzapine treatment. While modest triglyceride increases were described with early typicals, the large increases seen with clozapine-, olanzapine-, and quetiapine-treated patients are likely related to the distinct pharmacology of the atypicals. Cases of severe hyperlipidemia have been reported among most atypicals, except for risperidone. In a study of 4 clozapine-treated patients with hypertriglyceridemia, it was reported that the triglycerides normalized after switching to risperidone (59-61). Patients with elevated triglycerides are at risk for acute pancreatitis and long-term cardiovascular morbidity (59-61).

Hyperglycemia or Diabetes Mellitus
Reports of new-onset diabetes and diabetic ketoacidosis in patients treated with clozapine, olanzapine (28–30), and quetiapine (60) continue to accumulate. Among 82 patients treated with clozapine in a 5-year naturalistic study, 37% were diagnosed with adult-onset diabetes, and 72% of them went on to require oral hypoglycemic agents or insulin therapy for their glucose dysregulation (60). Since 1994, most studies of the emergence of hyperglycemia and diabetes during treatment with atypical antipsychotics involved clozapine (n = 20), followed by olanzapine (n = 13), quetiapine (n = 3) and risperidone (n = 4). Most frequently, hyperglycemia was not dosage-dependent and was reversible with cessation of treatment with olanzapine and clozapine but reappeared after reintroduction of the drug (60).

Schizophrenia is a known risk factor for adult-onset diabetes mellitus (60). Therefore, the risk is enhanced with neuroleptics, particularly olanzapine and clozapine, but also with some low-potency conventional neuroleptics. Diabetes-associated morbidity includes such problems as cardiovascular disease, cerebrovascular disease, and renal disease and leads to a significant increased risk of mortality (60). Ziprasidone and aripiprazole appear to be associated with a relatively low risk for hyperlipidemia and are relatively weight-neutral (61).

Issue with general schizophrenia research
Still, there is a great deal of suspicion where schizophrenia treatment is concerned. There is not as of yet a clear understanding of what schizophrenia is and how it affects the brain. A large number of patients still do not respond adequately to medication. Clozapine was a previously forgotten medicine that was reintroduced when it was found how to prevent agranulocytosis. Risperidone and olanzapine were descendants of clozapine that had no potential for causing agranulocytosis.

These medications were introduced quickly in the late 1980's and early 1990's as alternatives to conventional neuroleptics. It is regularly accepted that these medications have a lower chance of causing extrapyramidal symptoms. The research generally compares these medications to haloperidol, which generally has the highest likelihood of causing these symptoms, rather than the more commonly used chlorpromazine. In the psychiatric studies, it is supposedly a double-blind condition, so that neither the patient nor the doctor is to know who is getting the experimental treatment and who is getting the control treatment.

Nevertheless, the sudden occurrence of extrapyramidal effects in the patients receiving haloperidol makes it immediately clear which is the control group and which is the experimental group (63).

The aspect of schizophrenia most closely studied is the symptomatology, and to a far lesser extent, the behavior resulting from psychiatric symptomatology. Yet, the most important aspect of a deinstitutionalized life of a patient with schizophrenia is the ability to function socially.

This aspect is almost never studied. There is some concern that the atypical neuroleptics may not be safe for long-term use, and some report that the extrapyramidal effects do eventually occur with long-term use (64). Novel neurotransmitter mechanisms other than serotonin and dopamine for therapeutic strategies in schizophrenia beyond positive symptoms are important research issues for psychopharmacologists. Several recent studies have indicated promising results with neurotensin antagonists, purinergic agents, alpha-7-nicotinic cholinergic agonists, and glutametergic compounds (65). Rapidly advancing

research into schizophrenia includes diverse etiological hypotheses, and offers directions for future research and treatments.

Conclusion

Schizophrenia is a clinically heterogeneous disorder and is believed to be the common syndrome resulting from a number of different etiopathogenic processes. The advent of novel antipsychotics during the last 15 years represents a significant improvement over the effectiveness of conventional antipsychotics. However, these agents are not a magic bullet and are associated with their own treatment complications. For all these reasons, advances in the treatment of schizophrenia have been and continue to be urgently needed.

Acknowledgments

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