REVIEW ARTICLE

DRUG THERAPY

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Schizophrenia

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SCHIZOPHRENIA IS A CHRONIC, DEBILITATING PSYCHOTIC MENTAL DISorder that affects about 1 percent of people. A new generation of medications and recent developments in neuropathology, brain imaging, and molecular genetics have led to a greater understanding of the pathophysiology of schizophrenia and to improved treatment. Nonetheless, it remains an enigmatic illness that places a substantial burden on patients, their families, and society.

CLINICAL CHARACTERISTICS

Schizophrenia has varied and ominous symptoms that generally begin in late adolescence or early adulthood and usually continue throughout life.[1] Most patients have a history of behavioral dysfunction — primarily social and learning difficulties.[2] Diagnostic features of schizophrenia include auditory hallucinations (generally voices that converse with or about the patient) and delusions (often the paranoid belief that external forces are conspiring against the patient). Patients may have some insight that the voices are internal thoughts and that the delusions cannot possibly be true, but these phenomena remain persistent and troubling. In addition to these overt psychotic, or "positive," symptoms, various deficits, or "negative" symptoms, occur, including an inability to pay attention, the loss of a sense of pleasure, the loss of will or drive, disorganization or impoverishment of thoughts and speech, flattening of affect, and social withdrawal (Table 1). Positive and negative symptoms vary in intensity over time; patients may have predominantly one type at any particular time. Cognitive dysfunction, including a decreased ability to focus attention and deficiencies in short-term verbal and nonverbal memory, is also a core feature of the illness, which predicts vocational and social disabilities for patients.[3] Criminal behavior per se is not a concomitant of schizophrenia, but patients may commit violent acts in response to hallucinations or delusions or because of frustration in social interactions.[4] The lifetime prevalence of suicide is about 10 percent among patients with schizophrenia.[5]

PATHOPHYSIOLOGY

Schizophrenia is a uniquely human illness. Although none of us know to what extent our perception of the world is merely a construct of our own minds, persons with schizophrenia are confronted with this existential dilemma throughout most of their lives.[6] Their struggle to decide if the voices or suspicions they experience are real is part of their inability to discern relevant information from their surroundings. Indeed, the hallucinations and delusions, which initially seem mysterious, can often be traced to misprocessed information. Persons with schizophrenia are hypervigilant, responding to extraneous stimuli as well as to internal thoughts that most other persons can ignore.[7] In

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Table 1. Diagnostic Features of Schizophrenia.*

At least two of the following characteristic symptoms lasting at least one month: Delusions Hallucinations Disorganized speech Grossly disorganized or catatonic behavior Negative symptoms, such as affective flattening (Only one characteristic symptom is required if delusions are bizarre or hallucinations consist of a voice keeping up a running commentary on the person's behavior or thoughts or two or more voices conversing with each other)
Dysfunction in work, interpersonal relationships, or self-care throughout most of the illness; a level of functioning markedly below the level the patient had achieved or might reasonably have been predicted to achieve before the onset of illness
Any of the above symptoms lasting, in full or attenuated form, at least six months
Mood disorder not prominent after the onset of psychotic symptoms (if psychotic symptoms always occur during mood disturbance severe enough to meet the criteria for bipolar disorder or a major depressive disorder, the diagnosis is schizoaffective disorder)
Illness not due to a medication or other medical conditions or substance abuse
Illness not part of autism or another pervasive developmental disorder

* Adapted from the criteria of the American Psychiatric Association.[1]

addition to this deficit in sensory gating, patients have difficulty processing information in short-term memory to assess its significance.[8] For example, a college student who is becoming psychotic may report that he hears strange people who are hiding in the walls, whispering about his appearance. This symptom demonstrates his inability to filter out the noise of the dormitory and his lack of the skills necessary to learn the identity of the other students around him — both of which heighten his insecurity about himself.

SCHIZOPHRENIA AND DOPAMINE

The conceptualization by biomedical researchers of schizophrenia as the manifestation of deficits in elementary brain processes was facilitated by observations of certain drug effects. Many drugs that cause psychoses resembling schizophrenia (e.g., stimulants) increase dopaminergic neurotransmission. All currently available antipsychotic drugs that alleviate symptoms of schizophrenia decrease dopaminergic neurotransmission.[9] Decreased dopaminergic neurotransmission, in turn, diminishes the distractibility that characterizes patients with schizophrenia and improves their perceptual abilities.[10] Patients treated with such drugs concomitantly experience a decrease in the intensity of their hallucinations and delusions, and the patients are therefore better able to manage their behavior.[11]

The dopamine theory of schizophrenia has several flaws, however. First, blockade of dopaminergic neurotransmission does not fully alleviate symptoms of schizophrenia. Second, although positive symptoms of schizophrenia are diminished when dopaminergic neurotransmission is decreased by antipsychotic medications, levels of dopamine metabolites and receptors, when measured in patients before and after treatment, are still generally within the wide range of normal values.[12,13] Third, the role of dopamine in the brain is more complex than that of acting as a simple switch for psychotic symptoms. During acute psychotic episodes, many persons with schizophrenia appear to have increased occupancy of receptors in the basal ganglia by dopamine, as measured by the displacement of radioactive ligands on single-photon-emission computed tomography.[14] However, decreased dopaminergic activity in the cerebral cortex of the frontal lobe may also be one of the factors contributing to the cognitive impairment commonly found in persons with schizophrenia.[15] Investigation of the pathophysiology of schizophrenia has therefore extended beyond dopamine, and researchers exploring the pharmacologic treatment of schizophrenia, while not abandoning dopamine as a target, have extended their field of inquiry to include other neurotransmitters.

EVIDENCE OF MULTIPLE TYPES OF BRAIN DYSFUNCTION

No single lesion in the brain appears to be responsible for causing schizophrenia. Rather, multiple genetic and environmental factors contribute to disturbances in brain function and development that result in schizophrenia.[16] Inhibitory interneurons

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are particularly affected, as shown by a quantifiable decrease in their number, diminished expression of the enzymes that synthesize the inhibitory neurotransmitter γ-aminobutyric acid, diminished expression of neuropeptides such as cholecystokinin and somatostatin that are released during neurotransmission, and decreased migration of neurons into the cortex from the underlying white matter.[17-19] In addition to these specific changes in interneurons, there is a general loss of cortical neuropil, defined as the dendrites and axons that connect neurons, reflecting the failure of both pyramidal and inhibitory neurons to form synaptic connections.[20] In some areas of the brain, the total number of neurons is diminished as well.[21]

In a finding consistent with this neuropathology, magnetic resonance imaging (MRI) shows enlarged ventricles and diminished volume in several regions of the brain, including the hippocampus and the superior temporal cortex.[22] Analysis with magnetic resonance spectroscopy suggests diminished neuronal content in both the hippocampus and the prefrontal cortex, as indicated by levels of the neuronal amino acid N-acetylaspartate.[23] Despite apparently diminished brain tissue, functional brain imaging by means of positron-emission tomography and functional MRI reveal hyperactivity in the hippocampus and dorsal lateral prefrontal cortex, perhaps consistent with the loss of inhibitory neuron function.[24,25]

GENETIC FINDINGS IN SCHIZOPHRENIA

The diversity of neurobiologic findings in schizophrenia is mirrored by the multiplicity of genetic findings. Genetic epidemiologic findings, such as greater concordance with respect to schizophrenia among monozygotic twins than among dizygotic twins and a high incidence of illness among adopted children whose biologic mothers have schizophrenia, point to a significant heritable component that accounts for about 70 percent of the risk.[16] However, schizophrenia does not appear to be monogenic, and there are a number of chromosomal loci for which linkage to the illness has been replicated.[26] Single-nucleotide polymorphisms associated with schizophrenia, some of which have been shown to diminish neuronal functions, have been found in genes within these loci, including a G-protein regulator on chromosome 1, a protein on chromosome 6 associated with synaptic structure, a growth factor on chromosome 8 associated with synaptic growth, a response modulator on chromosome 13 that influences N-methyl-D-aspartate glutamate, a receptor on chromosome 15 for acetylcholine, and an enzyme on chromosome 22 that affects dopamine metabolism.[25,27-31] The glutamatergic, cholinergic, and dopaminergic neuronal mechanisms affected by these genetic factors have been related to various aspects of cognitive dysfunction involving the inability to perceive and remember information.[25,31]

In addition to the genetic factors, the environmental component of the pathogenesis of schizophrenia, accounting for the remaining 30 percent of the risk, includes perinatal and childhood brain injury and psychosocial stress over life events such as separation from the family.[32,33]

PATHOPHYSIOLOGY AND PHARMACOLOGIC TREATMENT

An acute psychotic episode in a person with schizophrenia appears to reflect a convergence of pathologic processes that can include an increase in the neurotransmission of dopamine (perhaps in response to stress), one or more genetic factors that alter the neurotransmitter mechanisms regulating the activity of cortical neurons, and nongenetic factors that have caused a loss of neurons and their connections. The result is a brain that is hypersensitive to stimuli and unable to regulate its response through normal inhibitory mechanisms. The decrease in the number of neurons and interneuronal connections that store and process information further diminishes the ability of the brain to sort the incoming information into what is known and what is unknown. Persons with schizophrenia therefore experience the world as overwhelming and commonly form the delusion that an evil force is controlling them or the world around them, or both.

The pharmacologic approach to this manifestation of psychosis has centered on the neurotransmitters that control the response of neurons to stimuli. Neurons that store and process information, such as the pyramidal neurons found in the cerebral cortex, are regulated by many other neurons. Inhibitory interneurons, which regulate cortical neurons, are a primary source of such regulation. The interneurons monitor and inhibit pyramidal-neuron activity. The activity of both pyramidal and inhibitory neurons is further modulated by dopaminergic neurons, as well as by serotonergic, cholinergic, and noradrenergic neurons, which send afferents into the cortex (Fig. 1). The receptors for dopamine, serotonin, and acetylcholine provide additional targets for newer antipsychotic drugs (Table 2).

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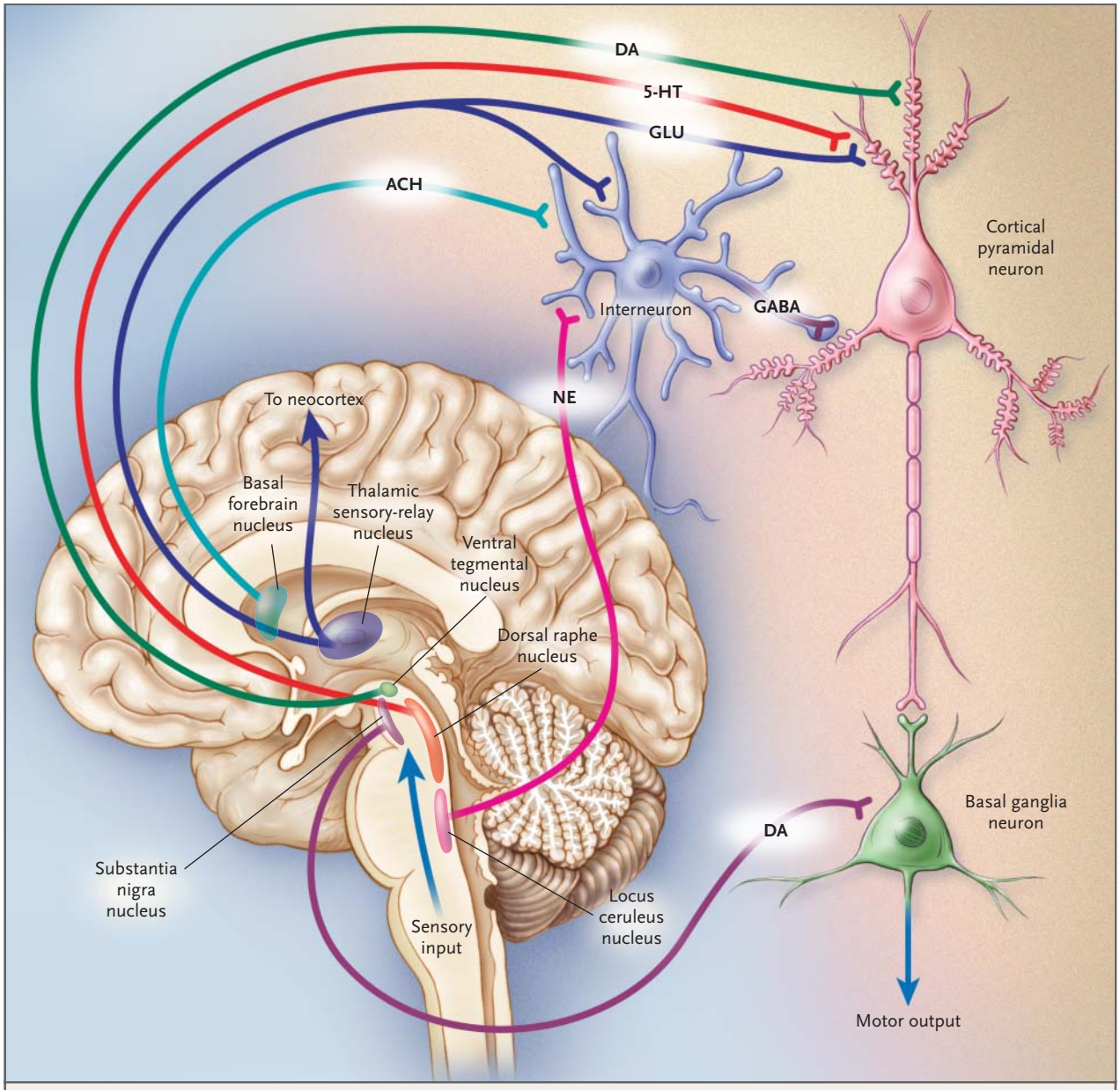

Figure 1. Neuronal Circuits That Appear to Be Involved in Schizophrenia and Its Treatment.

Thalamic nuclei relay sensory information to networks of pyramidal neurons in the limbic cortex and neocortex through glutaminergic excitatory afferents. An excessive response of pyramidal neurons is a putative mechanism of psychosis, which is consistent with reports from patients of overstimulation.[7] Various subcortical nuclei facilitate the response of principal neurons. Dopamine (DA) from the ventral tegmental nucleus activates D1 and D2 receptors that increase neuronal responses to glutamate (GLU).[34] Serotonin (5-hydroxytryptamine, or 5-HT) from the dorsal raphe nucleus activates 5-hydroxytryptamine 5-HT_{2A} receptors that facilitate the release of glutamate from synaptic terminals.[35] Antipsychotic drugs block the facilitative effects of both dopamine and serotonin.[36] Antipsychotic drugs also block dopamine from the substantia nigra nucleus in the basal ganglia and thus can cause movement disorders.[9] Interneurons in the cerebral cortex regulate the release of glutamate and thus the excitation of pyramidal neurons, through presynaptic inhibitory γ-aminobutyric acid (GABA) receptors.[37] Interneurons themselves are activated by glutamate, especially by way of receptors of the *N*-methyl-D-aspartate type.[38] Clozapine increases interneuron activity by increasing the release of acetylcholine (ACH) from the basal forebrain nucleus,[39] which activates interneurons through nicotinic cholinergic receptors,[40] and by blocking locus ceruleus nucleus activation of norepinephrine (NE) receptors, which decrease interneuron activity.[41] This simplified diagram omits other subcortical and cortical pathways.

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Table 2. Putative Neuronal Mechanisms in Psychosis and Its Treatment.

Mechanism	Type of Agent	Result
Pharmacologic Agents That Cause Psychosis, Hallucinations, or Delirium by Increasing the Response of Pyramidal Neurons in the Cerebral Cortex to Incoming Stimuli		
Dopamine agonism	Stimulant (cocaine, amphetamine)	Increased pyramidal-neuron response to glutamate excitation
Norepinephrine agonism	Stimulant (cocaine, amphetamine)	Decreased interneuron regulation of glutamate excitation of pyramidal neurons
Serotonin agonism	Hallucinogenic (lysergic acid diethylamide)	Presynaptic facilitation of glutamate release onto pyramidal neurons
Glutamate *N*-methyl-D-aspartate antagonism	Dissociative anesthetic (phencyclidine)	Diminished glutamatergic activation of interneurons, which increases excitation of pyramidal neurons
Acetylcholine antagonism	Anticholinergic (atropine)	Decreased cholinergic stimulation of interneurons, which increases excitation of pyramidal neurons
Antipsychotic Agents That Decrease Neuronal Response in the Cerebral Cortex to Incoming Stimuli		
Mechanism	Type of Agent	Result
Dopamine D2 antagonism	First-generation (haloperidol)	Blockade of dopamine facilitation of pyramidal-neuron response
D2 and 5-HT_{2A} antagonism	Second-generation (olanzapine, risperidone, quetiapine, ziprasidone)	Blockade of dopamine facilitation of pyramidal-neuron response and serotonin facilitation of glutamate release
Multiple actions	Clozapine	D1, D2, and 5-HT_{2-3} antagonism, leading to decreased pyramidal-neuron responses; increased acetylcholine release and norepinephrine antagonism, leading to increased interneuron regulation of pyramidal neurons
Mixed dopaminergic agonism and antagonism	Aripiprazole	Facilitation of low-level stimulation of dopamine receptors, blockade of higher levels of stimulation
Dopamine D2 and D3 antagonism	Amisulpride	Blockade of cortical dopamine receptors, but not those in basal ganglia

ANTIPSYCHOTIC TREATMENT

FIRST-GENERATION ANTIPSYCHOTIC AGENTS

The first antipsychotic, or neuroleptic, drug used to treat schizophrenia was chlorpromazine (Table 3). Its antipsychotic effects were identified incidentally, when it was tested as an antihistamine in subjects who happened to have schizophrenia.[11] Later research established that blockade of dopamine receptors is the therapeutic mechanism for the effectiveness of chlorpromazine in schizophrenia and prompted the development of increasingly potent dopamine antagonists.[9,43] Drugs such as haloperidol are more than 100 times as potent as chlorpromazine as antipsychotic agents, but they also are more likely to have parkinsonian side effects caused by dopamine blockade in the basal ganglia. Furthermore, despite their increasing potency, newer drugs in this group of first-generation agents that block dopamine receptors are no more effective than chlorpromazine.

Efficacy

Initial administration of first-generation antipsychotic drugs such as haloperidol and chlorpromazine in a patient with schizophrenia results in an immediate blockade of dopamine D2 receptors and a partial antipsychotic effect.[44] Further therapeutic effects develop over the course of six to eight weeks, a period of time that correlates with decreased release of dopamine from presynaptic terminals.[12,45] About 20 percent of patients have complete remission of their symptoms.[46] Most patients have some response but also have continuing symptoms. However, many severe, chronic syndromes associated with schizophrenia, such as catatonic withdrawal, that were observed before the era of commonly prescribed antipsychotic agents are rarely seen today, perhaps because of drug treatment. After an episode of psychosis, continued treatment with antipsychotic agents can significantly decrease the probability of relapse. Several reports of two-year studies showed that approximately 30 percent of patients

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have a relapse during treatment with first-generation antipsychotic drugs, as compared with 80 percent without treatment.[46-48]

Side Effects

Antipsychotic effects occur because of the blockade of neurotransmission between the dopaminergic neurons of the ventral tegmental area and the neurons in the limbic and cortical forebrain that perform higher-level information processing. However, the ventral tegmental neurons are members of an extensive family of neurons descended from a common embryologic ancestor that also use dopamine or related catecholamines, such as norepinephrine, as their neurotransmitter. The melanocytes, which synthesize melanin as a catecholamine polymer, are part of this family. The side effects of neuroleptic drugs encompass effects on the entire group of neurons of this lineage (Table 4).[49-53]

The most obvious side effects are involuntary movement disorders arising from the extrapyramidal system, many of which mimic the effects of Parkinson's disease and reflect the blockade of dopaminergic transmission between the dopaminergic neurons of the substantia nigra and the dorsal neostriatum.[9] Symptoms include dystonia, akathisia, bradykinesia, and tremor. Elderly patients may be at increased risk for hip fractures as a result of drug-associated movement disorders. As with all patients who have involuntary movement disorders, patients with schizophrenia are distressed but generally have difficulty describing the problem. Hence, they may appear in physicians' offices with vague reports of their symptoms.[54] Akathisia, a severe state of restlessness that is difficult to distinguish from agitation, is a major cause of noncompliance with the drug regimen. Treatment with propranolol (20 to 80 mg per day) is useful for controlling akathisia.[55] Bradykinesia, decreased spontaneous movement and slowed voluntary movement, mimics the effects of depression. Treatment with anticholinergic, antiparkinsonian drugs, such as benztropine (2 to 6 mg per day in divided doses), is helpful. Tardive dyskinesia, a choreoathetotic movement disorder, develops in about 30 percent of patients, generally after several years of treatment.[56] Orofacial movements such as grimacing are common manifestations. Tardive dyskinesia does not respond to anticholinergic agents; it resolves slowly after the withdrawal of first-generation drugs, but it may be irreversible.

Death caused by the administration of antipsychotic drugs is rare but can occur through several mechanisms. Temperature dysregulation can lead to a severe neuroleptic malignant syndrome, in which the patient's temperature exceeds 40°C (104°F) and brain death ensues. The occurrence of such an extreme outcome is related to both environmental heat and the presence of a Taq A polymorphism in the D2 dopamine-receptor genotype. Preventive measures include hydration and caution in the administration of anticholinergic agents in high-temperature environments, because the agents block perspiration.[57,58] Neuroleptic malignant syndrome is treated by rapid cooling, and dantrolene can be administered to inhibit the release of calcium in muscle cells and thus attenuate the metabolic changes caused by the hyperthermia. Dopamine agonists, such as bromocriptine, can be administered to reverse the pathogenic dopamine blockade.

A prolonged QT interval is a side effect of sev-

Table 3. Examples of Antipsychotic Drugs and Doses.*

Medication	Daily Oral Dose
	mg
First-generation antipsychotic agents	
Chlorpromazine (Thorazine)	150–1000
Perphenazine (Trilafon)	8–64
Trifluoperazine (Stelazine)	5–60
Thiothixene (Navane)	5–60
Haloperidol (Haldol)	2–25
Second-generation antipsychotic agents	
Clozapine (Clozaril)	100–900
Risperidone (Risperdal)	2–10
Olanzapine (Zyprexa)	5–20
Quetiapine (Seroquel)	75–750
Ziprasidone (Geodon)	40–160
Aripiprazole (Abilify)	15–30
Amisulpride† (Solian)	400–1200
	Intramuscular Dose (every 2–4 wk)
	mg
Depot preparations	
Fluphenazine decanoate (Prolixin decanoate injection)	12.5–50
Haloperidol decanoate (Haldol decanoate injection)	50–200
Flupentixol decanoate (Fluanxol depot injection)†	20–100
Risperidone microspheres (Risperdal Consta)‡	25–50

* Data are from Herz and Marder.[42]
† This drug is not available in the United States.
‡ This drug is not available in the United States in this form.

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Table 4. Common Side Effects of First-Generation and Second-Generation Antipsychotic Drugs.*

First-generation antipsychotics
Movement disorders, such as dystonia, bradykinesia, tremor, akathisia, choreoathetosis
Anhedonia
Sedation
Moderate weight gain
Temperature dysregulation, poikilothermy: cold in cold environments, warm in warm environments
Hyperprolactinemia, with galactorrhea and amenorrhea in women and gynecomastia in men; decreased sexual function in both
Postural hypotension
Sunburn
Prolonged QT interval, risk of potentially fatal arrhythmia (with thioridazine)
Second-generation antipsychotics
Moderate-to-severe weight gain (with olanzapine, clozapine)
Diabetes mellitus
Hypercholesterolemia
Sedation
Moderate movement disorder
Hypotension
Hyperprolactinemia (with risperidone)
Seizures (with clozapine)
Nocturnal salivation (with clozapine)
Agranulocytosis (with clozapine)
Myocarditis (with clozapine)
Lens opacities (with clozapine)

* Side effects can occur with any of the agents; a drug noted in parentheses indicates that a greater frequency of the side effect has been reported with that agent, but it can also occur with other agents.

eral antipsychotic drugs, and the possibility of this abnormality limits the dose of thioridazine, in particular. To what extent a prolonged QT interval predisposes a patient to the potentially fatal torsade de pointes arrhythmia is unknown, but the incidence of sudden death among patients treated with antipsychotic drugs is 0.015 percent per year — about twice the rate reported in the normal healthy population.[59]

SECOND-GENERATION ANTIPSYCHOTIC AGENTS

A second generation of antipsychotic agents has been introduced into clinical practice over the past 15 years in an attempt to improve therapeutic effects and decrease the side effects associated with first-generation dopamine-blocking drugs. All second-generation drugs share the D2 dopamine-receptor antagonism of first-generation drugs, but second-generation drugs are less tightly bound to the D2 receptor, and D2-receptor antagonism is no longer the sole therapeutic mechanism.[36,60] Hence, there are similarities in the general scope and time course of the effects of first- and second-generation drugs, but there are clinically important differences in both the therapeutic effects and the side effects.

Clozapine

Clozapine is the first atypical antipsychotic drug, so designated because it has antipsychotic effects without the adverse effects on movement of the first-generation drugs. In addition, clozapine has enhanced therapeutic efficacy, as compared with the first-generation drugs.[61] Therefore, it was introduced into clinical practice in the United States despite a serious known adverse effect: an increased incidence of agranulocytosis. Patients taking clozapine must undergo frequent monitoring of the leukocyte count (weekly for the first six months and every two weeks thereafter, including the first four weeks after the patient has discontinued the drug). Since the incidence of agranulocytosis is 0.39 percent and the death rate among patients who take clozapine is 0.013 percent,[62] dispensing by pharmacies must be linked to proof of monitoring to prevent patients from receiving the drug without adequate follow-up. Myocarditis has been reported in 0.032 percent of patients receiving clozapine, with a fatality rate of 0.012 percent.[63] Although all antipsychotic drugs lower the threshold for seizure, this effect is more pronounced with clozapine.[64] Nevertheless, for 30 percent of patients who do not have a response to other treatments, clozapine has substantially enhanced therapeutic effects that justify its use.[61,65] Clozapine reduces suicidal behavior, although a decrease in the rate of death by suicide has not yet been fully established.[66,67]

Clozapine has significant antagonist effects at D1, D2, and D4 dopamine receptors, as well as at norepinephrine and serotonin receptors. An unexpected effect is that patients who are smokers and who have a response to clozapine also decrease their cigarette smoking.[68] It has been hypothesized that heavy smoking among persons with schizophrenia is an attempt at self-medication, and indeed, nicotine does briefly improve several aspects of brain function.[69] Clozapine increases the synaptic release of acetylcholine, a fact that may account in part for its enhanced therapeutic effect, and concomitantly provides patients with an alternative to the use of nicotine, which is a cholinergic agonist.[39]

Newer Second-Generation Agents

The enhanced antipsychotic action of clozapine was initially thought to be due to its antagonism of

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both D2 dopaminergic and 5-hydroxytryptamine (5-HT) of type 2A (5-HT_{2A}) serotonergic receptors.[36] Drugs with a similar combined dopamine–serotonin antagonism — including risperidone, olanzapine, quetiapine, and ziprasidone — are all effective antipsychotic agents (Table 3). Like clozapine, these drugs have an efficacy that is equivalent to or exceeds the efficacy of first-generation antipsychotic agents, without many of the extrapyramidal effects of the first-generation drugs.[70-73] These newer agents also entail a greatly reduced risk of tardive dyskinesia.[74] Their increased efficacy with respect to negative schizophrenic symptoms is particularly noteworthy, and the rate of relapse is significantly less than that with the first-generation drugs.[73,75] For example, in a one-year, multisite trial, patients taking the second-generation drug risperidone had a 25 percent rate of relapse, as compared with a rate of 40 percent for patients taking the first-generation drug haloperidol.[73]

Other second-generation drugs have a different putative mechanism, involving refinements of action at dopamine receptors. Aripiprazole was characterized by mixed agonism and antagonism at dopamine receptors in preclinical studies, and investigators proposed that the drug enhanced low levels of dopaminergic transmission, thus improving cognition, but blocked higher levels of transmission that might cause psychosis. Aripiprazole also has effects at serotonergic receptors.[76] Amisulpride is an antagonist at D2 and D3 dopamine receptors.[77] Both aripiprazole and amisulpride have antipsychotic effects that are associated with a lower risk of movement disorder than that associated with first-generation agents.[77,78]

Side Effects

Although only clozapine causes agranulocytosis in a substantial proportion of patients, many second-generation drugs produce clinically significant weight gain — for example, 5.4 kg (11.9 lb) in a recent 14-week trial of olanzapine[79] (Table 4). Weight gain of 20 kg (44 lb) or more can occur with longer-term treatment. Diabetes mellitus has been increasingly reported in patients treated for more than five years with second-generation antipsychotic agents, presumably in association with weight gain; there is also some evidence of the development of insulin resistance.[80] In a few cases, life-threatening ketoacidosis has occurred. Cholesterol levels increase by 10 percent after 14 weeks of treatment with olanzapine.[81] Ziprasidone and amisulpride at recommended doses cause less weight gain than do other antipsychotic drugs.[72] Second-generation antipsychotic agents can sometimes induce obsessive–compulsive symptoms, which may reflect antagonism of serotonergic neurotransmission.[82]

Cognitive Improvement

The extent to which second-generation antipsychotic agents improve cognition in patients with schizophrenia is controversial.[83] First-generation antipsychotic agents have moderate effects on cognition, improving the patient's ability to pay attention to tasks.[10] Studies comparing first-generation and second-generation drugs show that about 30 to 70 percent of patients receiving second-generation drugs have improvement on neuropsychological tests of cognitive function, particularly in assessments of attention and short-term memory.[84] Improvement in these cognitive functions is seen in only 30 percent of patients receiving first-generation drugs.[84] The additional improvement in those receiving second-generation antipsychotic drugs, however, may not translate directly into an improved quality of life for all patients.[85] Furthermore, whether the difference in improvement in cognitive functions reflects the differential effects of the two groups of drugs on dopamine or on other neurotransmitters such as serotonin or acetylcholine is unknown. Low doses of haloperidol (5 mg per day), a first-generation antipsychotic drug, have effects on neurocognition equivalent to those of the second-generation drug risperidone, suggesting a positive effect from the blockade of low-level dopamine D2 receptors that was masked at the higher doses used for previous comparisons with second-generation agents.[86]

TREATMENT GUIDELINES

The treatment of schizophrenia requires experience in performing a differential diagnosis of mental disorders and in assessing a patient's potential for suicide and violence.[42,87] Optimal management includes psychological, social, and occupational therapies.[46,48] Physicians who are not psychiatrists are often consulted in the first stages of illness, and many chronically ill patients receive maintenance pharmacotherapy from their family physicians.

TREATMENT OF A FIRST PSYCHOTIC EPISODE

Immediate treatment of a patient after a first psychotic episode improves his or her long-term outcome and does not obscure the later differential diagnosis.[88] The usual presenting features are hallucinations or delusions, or both, generally ac-

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companied by anxiety, behavioral withdrawal, angry outbursts, and suicidal thoughts. Most psychiatrists initially prescribe a second-generation antipsychotic (other than clozapine, because of the incidence of side effects), in divided doses. Less disturbed sleep patterns and decreased anger and anxiety should be observed within the first day or two of treatment, with gradual improvement in other symptoms in the first week and near-maximal effects in six to eight weeks. Lack of improvement in the first one to four weeks should prompt an increase in the dose, followed by a change to another drug, usually clozapine or another second-generation drug after an additional four to six weeks, if the response remains inadequate. As in all illnesses in which suicidal intent is a factor, the patient's risk of death paradoxically increases as other symptoms improve.

MAINTENANCE TREATMENT

After the first episode has resolved, the patient should continue treatment for at least one year and then should be reevaluated. A variety of psychotherapeutic approaches are particularly helpful and can support the patient's rehabilitative efforts and increase insight about the illness. Many clinicians engage patients in weight-loss programs prospectively.

INDICATIONS FOR CLOZAPINE

Clozapine is not a first-line drug, because of the possibility of agranulocytosis. The indication for treatment with clozapine is either the lack of an adequate response with other second-generation or first-generation antipsychotic agents or the patient's inability to tolerate side effects, such as akathisia, of other antipsychotic agents. In practice, both highly functional and highly dysfunctional patients are prescribed clozapine.[89] Patients who are already highly functional sometimes have additional benefits, including a return to meaningful employment, that justify the increased risk of agranulocytosis, myocarditis, and seizures. Highly dysfunctional patients — for example, patients who have persistent, troubling psychotic and behavioral symptoms, including suicidal intent, despite treatment with other antipsychotic drugs — may respond to no other medication.

THE ROLE OF FIRST-GENERATION ANTIPSYCHOTIC AGENTS

Many patients continue to receive first-generation antipsychotic agents, and most treatment algorithms for patients with schizophrenia suggest a trial with a drug from this group for patients who do not have a response to second-generation drugs.[90] Patients receiving first-generation antipsychotic agents are monitored yearly for tardive dyskinesia. In most cases, tardive dyskinesia that is diagnosed early is reversed when the patient is switched to a second-generation drug. Tardive dyskinesia that involves involuntary tongue and chewing movements is more manageable if patients use good dental hygiene to retain their own teeth.

Antipsychotic drugs that are administered in a depot injection are associated with lower rates of relapse than medications that are administered orally, because of the greater likelihood that the patient will receive the medication.[48,91] Haloperidol and fluphenazine are available in the form of depot injections in the United States, and flupenthixol and risperidone are available as depot preparations in Europe.

THE CHOICE OF AN ANTIPSYCHOTIC DRUG

All antipsychotic drugs are effective for positive symptoms of acute psychosis. Second-generation drugs are preferred because of their greater effects on negative symptoms and cognitive function and because they are associated with a lower rate of relapse and a lower incidence of movement disorders. Consistent therapeutic differences among second-generation drugs, other than clozapine, have not been established; thus, the response of the individual patient must be used to guide selection.

First-generation antipsychotic agents administered as a depot injection, despite the risk of tardive dyskinesia, remain the optimal therapy for patients who have a relapse because of poor adherence to a regimen of oral medication.[49,91] Similarly, choosing to administer a drug with potentially fatal side effects, such as agranulocytosis and myocarditis, in the case of clozapine, is an acceptable treatment decision when patients have not had a response to other drugs. Furthermore, clozapine may be associated with a decreased risk of suicide; if so, the increase in mortality from agranulocytosis and myocarditis might be compensated for by the decrease in mortality from suicide, and clozapine could rationally be prescribed more frequently. The possibility of weight gain may influence the choice among second-generation drugs. For the patient in whom diabetes develops, ziprasidone may be an alternative. However, although ziprasidone is as effective as the first-generation drug haloperidol, its efficacy rela-

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tive to that of other second-generation drugs has yet to be evaluated.[72]

Antipsychotic drugs are often not the sole therapy for schizophrenia. Depression is common and is frequently treated with antidepressants.[92] Patients with schizoaffective symptoms who have periods of excitement and agitation that fulfill the criteria for mania are often treated with mood stabilizers such as lithium carbonate or valproic acid.[93] Patients with anxiety and sleep disturbance can be treated with benzodiazepines.[94]

EARLY INTERVENTION

The lower likelihood of extrapyramidal side effects associated with the second-generation antipsychotic drugs has made intervention earlier in life more acceptable to young patients and their parents.[95] A small number of the children with severe attention-deficit disorder and the teenagers with conduct disorder who are seen in primary care pediatric clinics already have most of the symptoms that make up a diagnosis of schizophrenia or bipolar disorder.[95-97]

Clinicians are often either reluctant to diagnose schizophrenia or unaware that it appears as early as six years of age. The presence of hallucinations and delusions is sometimes dismissed as childhood fantasy. However, affected children are deeply troubled and may be suicidal or even homicidal. They may have a good response to second-generation drugs, although weight gain can be particularly severe in this age group.[96] In addition, many children present with only subclinical signs of schizophrenia, including unmanageable aggressive reactions, psychosocial difficulties, attention and learning disabilities, and odd behavior. Because these symptoms are also typical of attention-deficit disorder, the children are frequently treated with stimulant drugs such as methylphenidate before overt symptoms of psychosis appear or are fully recognized. How stimulant treatment might contribute to the possibility of the later development of psychosis is unknown.

During adolescence and early adulthood, treatment with risperidone may delay the transition from the prodromal phase to the first episode of psychosis for at least six months.[97] The clinical importance of this delay in the longer term has not yet been established.[88] Delay of the onset of psychosis has historically been associated with an improved prognosis, but because psychosis does not ultimately develop in all children who have prodromal signs, the risk and benefit of such treatment are not clear.

The critical period for intervention may be quite early. Many of the genes that have been identified as candidates for contributing to schizophrenia are intimately involved with brain development, and deficits in brain development have been observed in the fetuses and newborn infants of women with schizophrenia.[98] Additional developmental abnormalities may occur through an exaggeration of the neuronal cell death that normally occurs in adolescence.[99] Interventions directed at problems during brain development have not yet been developed, but they may be a necessary part of the full treatment of schizophrenia.

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