and who maintain an emotional distance from others. Individuals have a restricted emotional range and remain socially isolated. Patients with schizotypal personality disorder frequently have unusual perceptual experiences and express magical beliefs about the external world. The essential feature of paranoid personality disorder is a pervasive mistrust and suspiciousness of others to an extent that is unjustified by available evidence. *Cluster B* disorders include antisocial, borderline, histrionic, and narcissistic types and describe individuals whose behavior is impulsive, excessively emotional, and erratic. *Cluster C* incorporates avoidant, dependent, and obsessive-compulsive personality types; enduring traits are anxiety and fear. The boundaries between cluster types are to some extent artificial, and many patients who meet criteria for one personality disorder also meet criteria for aspects of another. The risk of a comorbid major mental disorder is increased in patients who qualify for a diagnosis of personality disorder.

℞ PERSONALITY DISORDERS

Dialectical behavior therapy (DBT) is a cognitive-behavioral approach that focuses on behavioral change while providing acceptance, compassion, and validation of the patient. Several randomized trials have demonstrated the efficacy of DBT in the treatment of personality disorders. Antidepressant medications and low-dose antipsychotic drugs have some efficacy in cluster A personality disorders, while anticonvulsant mood-stabilizing agents and MAOIs may be considered for patients with cluster B diagnoses who show marked mood reactivity, behavioral dyscontrol, and/or rejection hypersensitivity. Anxious or fearful cluster C patients often respond to medications used for axis I anxiety disorders (see above). It is important that the physician and the patient have reasonable expectations vis-à-vis the possible benefit of any medication used and its side effects. Improvement may be subtle and observable only over time.

SCHIZOPHRENIA

Clinical Manifestations Schizophrenia is a heterogeneous syndrome characterized by perturbations of language, perception, thinking, social activity, affect, and volition. There are no pathognomonic features. The syndrome commonly begins in late adolescence, has an insidious (and less commonly acute) onset, and, often, a poor outcome, progressing from social withdrawal and perceptual distortions to recurrent delusions and hallucinations. Patients may present with positive symptoms (such as conceptual disorganization, delusions, or hallucinations) or negative symptoms (loss of function, anhedonia, decreased emotional expression, impaired concentration, and diminished social engagement) and must have at least two of these for a 1-month period and continuous signs for at least 6 months to meet formal diagnostic criteria. As individuals age, positive psychotic symptoms tend to attenuate and some measure of social and occupational function may be regained. "Negative" symptoms predominate in one-third of the schizophrenic population and are associated with a poor long-term outcome and a poor response to drug treatment. However, marked variability in the course and individual character of symptoms is typical.

The four main subtypes of schizophrenia are catatonic, paranoid, disorganized, and residual. Many individuals have symptoms of more than one type. *Catatonic-type* describes patients whose clinical presentation is dominated by profound changes in motor activity, negativism, and echolalia or echopraxia. *Paranoid-type* describes patients who have a prominent preoccupation with a specific delusional system and who otherwise do not qualify as having *disorganized-type* disease, in which disorganized speech and behavior are accompanied by a superficial or silly affect. In *residual-type* disease, negative symptomatology exists in the absence of delusions, hallucinations, or motor disturbance. The term *schizophreniform disorder* describes patients who meet the symptom requirements but not the duration requirements for schizophrenia, and *schizoaffective disorder* is used for those who manifest symptoms of schizophrenia and independent periods of mood disturbance. Prognosis depends not on symptom severity but on the response to antipsychotic medication. A permanent remission without recurrence does occasionally occur. About 10% of schizophrenic patients commit suicide.

Schizophrenia is present in 0.85% of individuals worldwide, with a lifetime prevalence of ~1–1.5%. An estimated 300,000 episodes of acute schizophrenia occur annually in the United States, resulting in direct and indirect costs of $62.7 billion.

Differential Diagnosis The diagnosis is principally one of exclusion, requiring the absence of significant associated mood symptoms, any relevant medical condition, and substance abuse. Drug reactions that cause hallucinations, paranoia, confusion, or bizarre behavior may be dose-related or idiosyncratic; parkinsonian medications, clonidine, quinacrine, and procaine derivatives are the most common prescription medications associated with these symptoms. Drug causes should be ruled out in any case of newly emergent psychosis. The general neurologic examination in patients with schizophrenia is usually normal, but motor rigidity, tremor, and dyskinesias are noted in one-quarter of untreated patients.

Epidemiology and Pathophysiology Epidemiologic surveys identify several risk factors for schizophrenia including genetic susceptibility, early developmental insults, winter birth, and increasing parental age. Genetic factors are involved in at least a subset of individuals who develop schizophrenia. Schizophrenia is observed in ~6.6% of all first-degree relatives of an affected proband. If both parents are affected, the risk for offspring is 40%. The concordance rate for monozygotic twins is 50%, compared to 10% for dizygotic twins. Schizophrenia-prone families are also at risk for other psychiatric disorders, including schizoaffective disorder and *schizotypal* and *schizoid personality disorders*, the latter terms designating individuals who show a lifetime pattern of social and interpersonal deficits characterized by an inability to form close interpersonal relationships, eccentric behavior, and mild perceptual distortions.

Despite evidence for a genetic causation, the results of molecular genetic linkage studies in schizophrenia are inconclusive. Major gene effects appear unlikely. Possible susceptibility genes include: neuregulin-1 (chromosome 8p21); dysbindin (6p22.3); proline dehydrogenase (22q11); D-amino-acid oxidase activator (13q34); disrupted in schizophrenia 1, (DISC1), (1q42); and catechol-*O*-methyl transferase (COMT). Neuregulin-1, dysbindin, and D-amino-acid oxidase activator appear to be involved in glutamatergic function, increasing interest in *N*-methyl-D-aspartate (NMDA)–mediated glutamate signaling as a possible therapeutic target for treatment. COMT is involved in the removal of dopamine from synapses, and DISC1 is a scaffolding protein that participates in a variety of protein-protein interactions important in neuronal development. One group has reported risk variants in the α7 nicotinic acetylcholine receptor subunit gene and linked it to a specific auditory processing deficit.

Schizophrenia is also associated with gestational and perinatal complications, including Rh factor incompatibility, fetal hypoxia, prenatal exposure to influenza during the second trimester, and prenatal nutritional deficiency. Studies of monozygotic twins discordant for schizophrenia have reported neuroanatomic differences between affected and unaffected siblings, supporting a "two-strike" etiology involving both genetic susceptibility and an environmental insult. The latter might involve localized hypoxia during critical stages of brain development.

A number of structural and functional abnormalities have been identified in schizophrenia, including (1) cortical atrophy and ventricular enlargement; (2) specific volume losses in the amygdala, hippocampus, right prefrontal cortex, fusiform gyrus, and thalamus; (3) progressive reduction in cortical volume over time; (4) reduced metabolism in the thalamus and prefrontal cortex; (5) abnormalities of the planum temporale; and (6) changes in the size, orientation, and density of cells in the hippocampus and prefrontal cortex, and decreased numbers of cortical interneurons. These observations have suggested that schizophrenia may result from a disturbance in a cortical striatal–thalamic circuit resulting in abnormalities in sensory filtering and attention.

Schizophrenic individuals are highly distractible and demonstrate deficits in perceptual-motor speed, ability to shift attention, and filtering out of background stimuli. Event-related evoked potential studies of schizophrenia have defined a reduction in P300 amplitude to a novel stimulus,

TABLE 386-14 ANTIPSYCHOTIC AGENTS

Name	Usual PO Daily Dose, mg	Side Effects	Sedation	Comments
First-Generation Antipsychotics				
Low-potency				
Chlorpromazine (Thorazine)	100–1000	Anticholinergic effects; orthostasis; photosensitivity; cholestasis; QT prolongation	+ + +	EPSEs usually not prominent; can cause anticholinergic delirium in elderly patients
Thioridazine (Mellaril)	100–600			
Clozapine (Clozaril)	150–600	Agranulocytosis (1%); weight gain; seizures; drooling; hyperthermia	+ +	Requires weekly WBC for first 6 months, then biweekly if stable
Mid-potency				
Trifluoperazine (Stelazine)	2–50	Fewer anticholinergic side effects; fewer EPSEs than with higher potency agents.	+ +	Well tolerated by most patients
Perphenazine (Trilafon)	4–64		++	
Loxapine (Loxitane)	30–100	Frequent EPSEs	+ +	
Molindone (Moban)	30–100	Frequent EPSEs	0	Little weight gain
High-potency				
Haloperidol (Haldol)	.5–20	No anticholinergic side effects; EPSEs often prominent	0/+	Often prescribed in doses that are too high; long-acting injectable forms of haloperidol and fluphenazine available
Fluphenazine (Prolixin)	1–20	Frequent EPSEs	0/+	
Thiothixene (Navane)	2–50	Frequent EPSEs	0/+	
Second-Generation Antipsychotics				
Risperidone (Risperdal)	2–8	Orthostasis	+	Requires slow titration; EPSEs observed with doses >6 mg qd
Olanzapine (Zyprexa)	10–30	Weight gain	+ +	Mild prolactin elevation
Quetiapine (Seroquel)	350–800	Sedation; weight gain; anxiety	+ + +	Bid dosing
Ziprasidone (Geodon)	120–200	Orthostatic hypotension	+/++	Minimal weight gain; increases QT interval
Aripiprazole (Abilify)	10–30	Nausea, anxiety, insomnia	0/+	Mixed agonist/antagonist

Note: EPSEs, extrapyramidal side effects; WBC, white blood count.

which implicates an impairment in cognitive processing. Impaired information processing is also found in unaffected family members.

The *dopamine hypothesis* of schizophrenia is based on the discovery that agents that diminish dopaminergic activity also reduce the acute symptoms and signs of psychosis, specifically agitation, anxiety, and hallucinations. Amelioration of delusions and social withdrawal is less dramatic. Thus far, however, evidence for increased dopaminergic activity in schizophrenia is indirect, although decreased D_2 receptor occupancy by dopamine has been shown in drug-naïve patients. An increase in the activity of nigrostriatal and mesolimbic systems and a decrease in mesocortical tracts innervating the prefrontal cortex is hypothesized, although it is likely that other neurotransmitters, including serotonin, acetylcholine, glutamate, and GABA, also contribute to the pathophysiology of the illness. Possible involvement of excitatory amino acids is supported by the genetic data cited above and findings that NMDA receptor antagonists and channel blockers, such as phencyclidine (PCP) and ketamine, produce characteristic signs of schizophrenia in normal individuals; cycloserine, an NMDA receptor agonist, can decrease the negative symptoms of psychosis.

SCHIZOPHRENIA

Antipsychotic agents **(Table 386-14)** are the cornerstone of acute and maintenance treatment of schizophrenia and are effective in the treatment of hallucinations, delusions and thought disorders, regardless of etiology. The mechanism of action involves, at least in part, binding to dopamine D_2/D_3 receptors in the ventral striatum; the clinical potencies of traditional antipsychotic drugs parallel their affinities for the D_2 receptor, and even the newer "atypical" agents exert some degree of D_2 receptor blockade. All neuroleptics induce expression of the immediate-early gene c-*fos* in the nucleus accumbens, a dopaminergic site connecting prefrontal and limbic cortices. The clinical efficacy of newer atypical neuroleptics, however, may involve NMDA receptor blockade, α_1- and α_2-noradrenergic activity, altering the relationship between $5HT_2$ and D_2 receptor activity, as well as faster dissociation of D_2 binding and effects on neuroplasticity.

Conventional neuroleptics differ in their potency and side-effect profile. Older agents, such as chlorpromazine and thioridazine, are more sedating and anticholinergic and more likely to cause orthostatic hypotension, while higher potency antipsychotics, such as haloperidol, perphenazine, and thiothixene, are more likely to induce extrapyramidal side effects. The model first-generation antipsychotic agent is *clozapine*, a dibenzodiazepine that has a greater potency in blocking the $5HT_2$ than the D_2 receptor and a much higher affinity for the D_4 than the D_2 receptor. Its principal disadvantage is a risk of blood dyscrasias. Unlike other antipsychotics, clozapine does not cause a rise in prolactin level. Approximately 30% of patients who do not benefit from conventional antipsychotic agents will have a better response to this drug, which also has a demonstrated superiority to other antipsychotic agents in preventing suicide; however, its side-effect profile makes it most appropriate for treatment-resistant cases. *Risperidone*, a benzisoxazole derivative, is more potent at $5HT_2$ than D_2 receptor sites, like clozapine, but it also exerts significant α_2 antagonism, a property that may contribute to its perceived ability to improve mood and increase motor activity. Risperidone is not as effective as clozapine in treatment-resistant cases but does not carry a risk of blood dyscrasias. *Olanzapine* is similar neurochemically to clozapine but has a significant risk of inducing weight gain. *Quetiapine* is distinct in having a weak D_2 effect but potent α_1 and histamine blockade. *Ziprasidone* causes minimal weight gain and is unlikely to increase prolactin but may increase QT prolongation. *Aripiprazole* also has little risk of weight gain or prolactin increase but may increase anxiety, nausea, and insomnia as a result of its partial agonist properties.

Antipsychotic agents are effective in 70% of patients presenting with a first episode. Improvement may be observed within hours or days, but full remission usually requires 6–8 weeks. The choice of agent depends principally on the side-effect profile and cost of treatment or on a past personal or family history of a favorable response to the drug in question. Atypical agents appear to be more effective in treating negative symptoms and improving cognitive function. An equivalent treatment response can usually be achieved with relatively low doses of any drug selected, i.e., 4–6 mg/d of haloperidol, 10–15 mg of olanzapine, or 4–6 mg/d of risperidone. Doses in this range result in >80% D_2 receptor blockade, and there is little evidence that higher doses increase either the rapidity or degree of response. Maintenance treatment requires careful attention to the possibility of relapse and monitoring for the development of a movement disorder. Intermittent drug treatment is less effective than regular dosing, but gradual dose reduction is likely to improve social functioning in many schizophren-

ic patients who have been maintained at high doses. If medications are completely discontinued, however, the relapse rate is 60% within 6 months. Long-acting injectable preparations (risperidone) are considered when noncompliance with oral therapy leads to relapses. In treatment-resistant patients, a transition to clozapine usually results in rapid improvement, but a prolonged delay in response in some cases necessitates a 6- to 9-month trial for maximal benefit to occur.

Antipsychotic medications can cause a broad range of side effects, including lethargy, weight gain, postural hypotension, constipation, and dry mouth. Extrapyramidal symptoms such as dystonia, akathisia, and akinesia are also frequent with first-generation agents and may contribute to poor adherence if not specifically addressed. Anticholinergic and parkinsonian symptoms respond well to trihexyphenidyl, 2 mg bid, or benztropine mesylate, 1–2 mg bid. Akathisia may respond to beta blockers. In rare cases, more serious and occasionally life-threatening side effects may emerge, including ventricular arrhythmias, gastrointestinal obstruction, retinal pigmentation, obstructive jaundice, and neuroleptic malignant syndrome (characterized by hyperthermia, autonomic dysfunction, muscular rigidity, and elevated creatine phosphokinase levels). The most serious adverse effects of clozapine are agranulocytosis, which has an incidence of 1%, and induction of seizures, which has an incidence of 10%. Weekly white blood cell counts are required, particularly during the first 3 months of treatment.

The risk of type 2 diabetes mellitus appears to be increased in schizophrenia, and second-generation agents as a group produce greater adverse effects on glucose regulation, independent of effects on obesity, than traditional agents. Clozapine, olanzapine, and quetiapine seem more likely to cause hyperglycemia, weight gain, and hypertriglyceridemia than other atypical antipsychotic drugs. Close monitoring of plasma glucose and lipid levels are indicated with the use of these agents.

A serious side effect of long-term use of first generation antipsychotic agents is *tardive dyskinesia*, characterized by repetitive, involuntary, and potentially irreversible movements of the tongue and lips (bucco-linguo-masticatory triad), and, in approximately half of cases, choreoathetosis. Tardive dyskinesia has an incidence of 2–4% per year of exposure, and a prevalence of 20% in chronically treated patients. The prevalence increases with age, total dose, and duration of drug administration. The risk associated with second-generation agents appears to be much lower. The cause may involve formation of free radicals and perhaps mitochondrial energy failure. Vitamin E may reduce abnormal involuntary movements if given early in the syndrome.

The CATIE study, a large scale investigation of the effectiveness of antipsychotic agents in "real world" patients, revealed a high rate of discontinuation of treatment over 18 months. Olanzapine showed greater effectiveness than quetiapine, risperidone, perphenazine, or ziprasidone but also a higher discontinuation rate due to weight gain and metabolic effects. Surprisingly, perphenazine, a first-generation agent, showed little evidence of inferiority to newer drugs.

Drug treatment of schizophrenia is by itself insufficient. Educational efforts directed toward families and relevant community resources have proved to be necessary to maintain stability and optimize outcome. A treatment model involving a multidisciplinary case-management team that seeks out and closely follows the patient in the community has proved particularly effective.

ASSESSMENT AND EVALUATION OF VIOLENCE

Primary care physicians may encounter situations in which family, domestic, or societal violence is discovered or suspected. Such an awareness can carry legal and moral obligations; many state laws mandate reporting of child, spousal, and elder abuse. Physicians are frequently the first point of contact for both victim and abuser. Approximately 2 million older Americans and 1.5 million U.S. children are thought to experience some form of physical maltreatment each year. Spousal abuse is thought to be even more prevalent. An interview study of 24,000 women in ten countries found a lifetime prevalence of physical or sexual violence that ranged from 15–71%; these individuals are more likely to suffer from depression, anxiety, somatization disorder, and substance abuse and to have attempted suicide. In addition, abused individuals frequently express low self-esteem, vague somatic symptomatology, social isolation, and a passive feeling of loss of control. Although it is essential to treat these elements in the victim, the first obligation is to ensure that the perpetrator has taken responsibility for preventing any further violence. Substance abuse and/or dependence and serious mental illness in the abuser may contribute to the risk of harm and require direct intervention. Depending on the situation, law enforcement agencies, community resources such as support groups and shelters, and individual and family counseling can be appropriate components of a treatment plan. A safety plan should be formulated with the victim, in addition to providing information about abuse, its likelihood of recurrence, and its tendency to increase in severity and frequency. Antianxiety and antidepressant medications may sometimes be useful in treating the acute symptoms, but only if independent evidence for an appropriate psychiatric diagnosis exists.

MENTAL HEALTH PROBLEMS IN THE HOMELESS

There is a high prevalence of mental disorders and substance abuse among homeless and impoverished individuals. Depending on the definition used, estimates of the total number of homeless individuals in the United States range from 800,000 to 2 million, one-third of whom qualify as having a serious mental disorder. Poor hygiene and nutrition, substance abuse, psychiatric illness, physical trauma, and exposure to the elements combine to make the provision of medical care challenging. Only a minority of these individuals receive formal mental health care; the main points of contact are outpatient medical clinics and emergency departments. Primary care settings represent a critical site in which housing needs, treatment of substance dependence, and evaluation and treatment of psychiatric illness can most efficiently take place. Successful intervention is dependent on breaking down traditional administrative barriers to health care and recognizing the physical constraints and emotional costs imposed by homelessness. Simplifying health care instructions and follow-up, allowing frequent visits, and dispensing medications in limited amounts that require ongoing contact are possible techniques for establishing a successful therapeutic relationship.

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