Clinical Review

Schizophrenia

Wayne Katon, MD, and Richard Ries, MD
Seattle, Washington

The diagnostic criteria for schizophrenia have been extensively changed by the third edition of the *Diagnostic and Statistical Manual of Mental Disorders*, recently adopted by the American Psychiatric Association (DSM III). To receive this diagnosis, the patient must have onset of illness before age 45 years, have had a chronic course, manifest the presence of characteristic symptoms, such as delusions, hallucinations, or loose associations during a phase of the illness, and have experienced a downhill social and vocational course; affective disorders and organic brain syndrome must be carefully excluded. The utilization of this "narrow" definition has caused a major shift toward increasing the diagnosis of affective disorders and decreasing the diagnosis of schizophrenia in the United States.

The etiology of schizophrenia is still uncertain, but recent research has elucidated one subgroup of schizophrenic patients who have subtle indices of neurological damage and a clinical course similar to that found in dementia. Dopamine excess in the mesolimbic system is the predominant inferred cause for the majority of schizophrenia cases, and antipsychotic medications all rely on dopamine receptor blockade for their efficacy. Antipsychotic medications are effective in schizophrenia but are less potent against such negative symptoms as apathy, neglect of personal hygiene, and social withdrawal.

Schizophrenia has puzzled medical practitioners for many centuries. In the past it became almost synonymous with such terms as mental illness, nervous breakdown, and psychosis because of imprecise diagnostic boundaries. As recently as 1970, studies demonstrated that American psychiatrists were diagnosing schizophrenia more than two times as frequently as their English contemporaries.[1,2] American psychiatrists had a much broader definition of schizophrenia, tending to use this diagnosis in cases that English psychiatrists labeled as having affective disorders (manic-depressive illness or depression) or personality disorders. With the advent of revolutionary psychiatric medications such as neuroleptics, lithium,

From the Division of Consultation-Liaison Psychiatry, Department of Psychiatry and Behavioral Sciences, and the Department of Family Medicine, School of Medicine, University of Washington, Seattle, Washington. Requests for reprints should be addressed to Dr. Wayne Katon, Department of Psychiatry and Behavioral Sciences, RP-10, School of Medicine, University of Washington, Seattle, WA 98195.

Table 1. DSM III Diagnostic Criteria for Schizophrenic Disorders

1. At least one of the following during a phase of the illness:
   - Bizarre delusions (content is patently absurd and has no possible basis in fact), such as delusions of being controlled, thought broadcasting, thought insertion, or thought withdrawal
   - Somatic, grandiose, religious, nihilistic, or other delusions without persecutory or jealous content
   - Delusions with persecutory or jealous content if accompanied by hallucinations of any type
   - Auditory hallucinations in which either a voice keeps up a running commentary on the indvidual's behavior or thoughts or two or more voices converse with each other
   - Auditory hallucinations on several occasions with content of more than one or two words, having no apparent relation to depression or elation
   - Incoherence, marked loosening of associations, markedly illogical thinking, or marked poverty of content of speech if associated with at least one of the following: (1) blunted, flat, or inappropriate affect, (2) delusions or hallucinations, and (3) catatonic or other grossly disorganized behavior
2. Deterioration from a previous level of functioning in such areas as work, social relations, and self-care
3. Continuous signs of the illness for at least six months at some time during the person's life, with some signs of the illness at present. The six-month period must include an active phase during which there are symptoms from category 1, with or without a prodromal or residual phase
4. The full depressive or manic syndrome, if present, did not precede the psychotic symptoms, or it was brief in duration relative to the duration of the psychotic symptoms in category 1
5. Onset of prodromal or active phase of the illness before 45 years of age
6. Symptoms not due to any organic mental disorder or mental retardation

and antidepressants, more specific use of electroshock therapy, and the exponential growth of neuroendocrine and neurochemistry studies, it became essential for psychiatrists to establish accurate diagnostic guidelines so that specific diagnostic tests and treatments could be tested on homogeneous populations.

The Diagnostic and Statistical Manual of Mental Disorders (DSM III) has now firmly established research-tested diagnostic criteria for schizophrenia that have validity and reliability comparable to medical diagnosis.[3] This new definition is based on both inclusion and exclusion criteria as well as characteristic symptoms involving multiple psychological processes.

As can be seen in Table 1, not only are active symptoms such as hallucinations, delusions, loose associations, or blunted affect used to define the illness, but there must also be a deterioration from previous levels of functioning in work, social relations, and self-care; duration criteria requiring at least six months of continuous signs of illness also must be met.[3] In addition, if a full depressive or manic syndrome precedes the specific psychotic symptoms, the diagnosis of schizophrenia cannot be made. Thus schizophrenia has become a diagnosis of exclusion in which social deterioration and chronic course must occur, and major affective illness must first be ruled out. This development in diagnosis has evolved from research demonstrating that patients with affective psychosis (mania, depression), schizophreniform psychosis, and drug-induced psychosis are often indistin-

Continued on page 102

Continued from page 100

guishable from chronic schizophrenics when both are in an acute phase of psychosis.[4,5] Thus a manic patient can have hallucinations, delusions, loose associations, and bizarre behavior during an acute psychosis; however, when the course of manic-depressive illness is followed, it is a relapsing remitting illness.

The narrow definition of schizophrenia has caused a marked shift toward decreasing the frequency of the diagnosis of schizophrenia and increasing the frequency of the diagnosis of affective disorders (manic-depressive illness and major depression). Several studies utilizing either DSM III criteria for schizophrenia or a similar diagnostic system[6] have shown that only 6 percent of psychiatric inpatients in an urban acute care hospital can be diagnosed as schizophrenic, which is substantially lower than the 30 to 40 percent previously reported.[7,8] The most frequent diagnosis in these hospital studies was affective disorder; for instance, Ries et al[8] found that 23 percent of their psychiatric inpatients had major depressive disorder and 4 percent had manic-depressive illness. A detailed chart study of 525 psychiatric inpatients from the 1930s and 1940s revealed that 63 percent of the patients originally diagnosed as schizophrenic did not fulfill modern criteria for the illness because of short duration of symptoms, episodic course, or the presence of affective symptoms.[9] On the other hand, a high correlation was found between chart diagnosis and modern criteria for affective disorder, with only 25 percent of these past diagnoses discarded because of lack of symptoms necessary to correlate with research criteria. Taylor et al[5] examined 88 psychiatric patients with an admission diagnosis of schizophrenia and demonstrated that the patients who fulfilled criteria for "good-prognosis schizophrenia," ie, sudden onset (less than three months), precipitating event, clouded consciousness, broad affective range, and good premorbid social adjustment, were frequently indistinguishable from patients with manic-depressive illness. These good-prognosis schizophrenics presented clinically with affective symptoms, responded well to somatic treatments, had more affective illness and alcoholism in first-degree relatives, and frequently satisfied research criteria for manic-depressive illness. The importance of the above studies is that there is a large group of patients who have been labeled schizophrenic under the old broad definition who are misdiagnosed and apt to come to the attention of family physicians. It is incumbent on the family physician to gather data about clinical course (chronic vs episodic), social and vocational adjustment, family history, the presence of affective symptoms, the phenomenology of the illness, and response to prior treatment, and not assume the past diagnosis has been correct (Table 2). It is important to err diagnostically on the side of affective disorders, since treatment with antidepressants, lithium, and electric shock therapy may be curative, whereas treatment of schizophrenia utilizes different pharmacologic agents and is largely symptomatic.

Another development of the DSM III is the differentiation of the prodromal, active, and residual phases of schizophrenic illness.[3] During the prodromal phase there is a clear deterioration from a previous level of functioning. It is characterized by social withdrawal, peculiar behavior, impairment of functioning at work, in the family, and in self-care, blunted or inappropriate affect, disturbances in communication, bizarre ideation, and unusual perceptual experiences. A change in personality is often noted by friends or family. The length of this prodromal phase is quite variable and often insidious. Generally, the more insidious and long term the prodromal phase, the worse the prognosis.

During the active phase psychotic symptoms such as delusions, hallucinations, loose associations, incoherence, and behavior that is grossly disorganized or catatonic are present.

The residual phase, which follows the active phase, clinically resembles the prodromal phase. Affective flattening or blunting and impairment in role functioning tend to be more common in the residual phase. Psychotic symptoms such as hallucinations and delusions often persist but are no longer as florid as in the active phase. At time of diagnosis, patients may be in any one of these phases and may be observed to change from phase to phase or alternatively remain in a specific phase.

Prevalence and Incidence

Studies in Europe and Asia using relatively narrow criteria similar to those defined in the DSM III have found a prevalence rate from 0.2 percent to 1.0 percent.[3] Early studies in the United States using broader criteria and surveying urban populations

Continued on page 107

Table 2. Differentiating Manic-Depressive Illness from Schizophrenia

Manic-Depressive Illness	Schizophrenia
1. Acute onset of symptoms	1. Insidious onset
2. Premorbid good adjustment in vocational and social relationships	2. Premorbid social and vocational adjustment often poor with schizoid and paranoid personality
3. Broad range of affect	3. Blunted affect
4. Episodic course	4. Chronic course; ill continuously for more than six months
5. Presence of pre-existing manic or depressive symptoms preceding history of psychosis	5. Affective symptoms absent or develop after psychotic symptoms (loose associations, delusions, or hallucinations)
6. Family history of affective disorder or alcoholism	6. Family history of schizophrenia
7. Precipitating event	7. Insidious onset, often with no precipitating events
8. Can have Schneiderian first-rank symptoms, but less frequently	8. More likely to have Schneiderian first-rank symptoms
9. Usually married	9. Often single, especially men

have reported higher rates (1 to 2 percent).[10] The incidence of schizophrenia has ranged from .043 to .069 percent in the United States over the last 25 years, yielding 92,450 to 148,350 new cases each year.[10]

Premorbid History

The diagnosis of schizophrenia cannot be excluded on the basis of the patient's prepsychotic history, which can be of any variety. However, many schizophrenics have a history of early childhood asocial development, learning deficits, poor peer relationships, and emotional eccentricity.[11] In these preschizophrenic children the child's meager attempts at group involvement are so blundering, undiplomatic, and unusual that they often lead to social ostracism and scapegoating. At least some of these children suffer from minimal brain damage.

It is unclear how many children with asocial development do not develop psychotic episodes or how frequently this pattern occurs in schizophrenics; however, such a history in a schizophrenic patient is a powerful predictor of future poor function. This premorbid asocial pattern has also been linked to a variety of neuropsychiatric indices of brain damage that will be covered below.

Differential Diagnosis

Schizophrenia must be differentiated from delirium, dementia, and organic diseases presenting as psychiatric syndromes (Table 3). In delirium the presence of disorientation, fluctuating levels of consciousness, diffuse slow waves on electroencephalogram, and an underlying medical illness (high fever, metabolic abnormalities, hypoglycemia, hypoxia) are diagnostic.[12] Dementia in a middle-aged to elderly person is characterized by insidious onset of initial decline in short-term memory and lack of ability to abstract, followed by a general decline in all cognitive functions. Dementia and delirium can usually be differentiated from schizophrenia by a careful mental status examination.

Table 4 lists the most common organic illnesses that cause psychiatric illness.[13] Careful mental status examination, prior history of one of these organic illnesses, and a high index of suspicion for underlying disease are essential to diagnose organic illness masquerading as a psychosis.

Table 3. Differential Diagnosis

- Organic brain syndrome
  - Delirium
  - Dementia
- Organic disease presenting as psychosis
  - Endocrinopathies: hyposecretion or hypersecretion of thryoid, parathyroid, adrenal cortex
  - Metabolic abnormalities: acute porphyria, pernicious anemia, Wilson's disease, hypoglycemia
  - Neoplastic conditions: intracranial tumor, pancreatic carcinoma, pheochromocytoma
  - Systemic lupus erythematosus, multiple sclerosis
- Drug-induced psychosis
  - Amphetamine
  - Phencyclidine
  - LSD
  - Cocaine
  - Mescaline
  - Alcoholic hallucinosis
- Idiosyncratic medication side effect
- Manic-depressive illness
- Psychotic depression
- Paranoid disorders
- Schizophreniform disorder
- Personality disorders: schizotypal, borderline, schizoid
- Mental retardation
- Factitious disorder with psychotic syndrome

Psychoses secondary to drug abuse or as idiosyncratic responses to prescribed medication are very common. A recent review of the most common medications causing psychiatric symptomatology has been published by the *Medical Letter*.[14] Several recent studies have shown that almost one half of psychiatric patients less than 30 years of age had abused drugs at some time.[15] Drugs such as amphetamines, cocaine, lysergic acid diethylamide, and phencyclidine can uncover an underlying genetic susceptibility to schizophrenia or affective illness or cause a short-term psychosis in a patient without genetic susceptibility. Urine and serum toxicology screens are useful if there is a question of drug abuse. Compared with chronic psychotics, patients ill from drugs are more disorganized, less retarded in motor movement, less blunted in affect, and more excited, have better prior histories of socialization, are more intelligent, have better premorbid work records, and have considerably lower incidence of Schneiderian-positive signs: (1) audible thoughts, (2) voices heard arguing, (3) voices heard commenting on one's actions, (4) the experiences of external influences acting on the body, (5) thought withdrawal and other interferences with thought, (6) thought broadcasting, (7) delusional perception.[16]

Affective disorders (manic-depressive illness and psychotic depression) are the most common psychiatric disorders misdiagnosed as schizophrenia. It is often difficult to differentiate these disorders because psychotic symptoms (delusions, hallucinations, loose associations) may occur in both illnesses during the acute phase.[4]

Patients with manic-depressive illness are best differentiated from schizophrenics by a history of mood fluctuations, or an episodic vs a chronic course, and better work and social function. Other features are described in Table 2. In psychotic depression the depressed mood and associated vegetative symptoms (anorexia, weight loss, insomnia or hypersomia, loss of interest in activities, loss of energy, diminished ability to think or concentrate) develop before psychotic symptoms. When delusions or hallucinations are present, their content usually involves themes of personal inadequacy, guilt, disease, death, nihilism, or deserved punishment.

Other psychiatric disorders in the differential diagnosis include paranoid disorders that involve the presence of a tight paranoid delusional system without the other signs of schizophrenia, and schizophreniform disorder in which the duration of illness is less than six months, although symptomatology may be similar to that of schizophrenia. Patients with personality disorders may develop transient psychotic episodes under overwhelming stress, returning within hours or days to the usual level of functioning. These episodes can also be seen in obsessive-compulsive disorder and mental retardation. Patients with factitious disorder may complain of hallucinations in order to be hospitalized, but they will show few of the disturbed psychological processes (Table 1).

Etiology

Current research supports the view of schizophrenia as a heterogeneous group of disorders

Continued on page 111

Continued from page 108

with a multifactorial etiology involving genetic, neuroendocrine, pathophysiologic, anatomic, and environmental components.

Genetic

The genetic evidence is consistent with the concept of schizophrenia as a disease. Whereas the general American population has a 1 percent lifetime risk of schizophrenia, a review of genetic studies by Tsuang and Vandermey[17] revealed that its risk increases with genetic relatedness to an affected family member. The incidence of schizophrenia in parents of schizophrenics is 5 percent, whereas schizophrenics' children and siblings have a 10 percent incidence. Risk is adjusted up or down depending on the number of relatives affected, age of onset of illness, and severity. Concordance for schizophrenia occurs in about one half of monozygotic twins, whereas approximately 10 percent of dizygotic twins are affected.[18,19] Yet since relatives of schizophrenics share many environmental influences in addition to their genetic endowments, both factors may be operational in the genesis of the disease. Most convincing of a genetic factor are the Danish studies of adopted children whose natural parents were schizophrenic.[20] These children have a higher incidence of schizophrenia than do adopted controls of normal parents. The biologic relatives of schizophrenic adopted children are also more likely to be schizophrenic than those of normal adopted children. Finally, children adopted by schizophrenic parents do not have increased rates of schizophrenia.

Neuroendocrinologic

Concordant with the genetic studies and supporting the biological model of schizophrenia is the evidence from pharmacological treatment studies. Pharmacology offers two approaches to the pathogenesis of a disorder: to examine the action of drugs that produce or mimic the disorders, and to investigate the mechanism of activity of drugs that ameliorate the disorder.[20] In the case of schizophrenia both courses of investigation have been pursued, and the hypothesis that certain central dopaminergic systems are overactive has developed.

Chronic amphetamine toxicity is characterized by paranoid psychosis with auditory hallucinations and stereotyped behavior but with little delirium or confusion. Although schizophrenic patients can recognize psychosis secondary to lysergic acid diethylamide as different from their usual symptoms, they are unable to differentiate an amphetamine psychosis.[20] Further, amphetamine, methylphenidate, and L-dopa can precipitate active schizophrenia in patients who are in the residual phase. The available evidence suggests that psychosis due to amphetamine use is mediated through the release and potentiation of dopamine and its receptors in the brain.[20]

While sedative agents and antianxiety drugs are no more effective than placebo in the treatment of schizophrenia, several different classes of drugs (phenothiazines, butyrophenones, thioxanthenes, dihydroindolones, and dibenzoxazepines) are effective and share the property of being potent dopamine blockers.[21] All the antipsychotic drugs work on the basis of dopamine receptor blockade, particularly in the mesolimbic system, yet not one of these drugs cures the disorder. At best they control many of the active phase symptoms. Other neurotransmitters, including acetylcholine and γ-aminobutyric acid, also appear to influence dopamine transmission and may be important in the etiology of schizophrenia.[22] Antipsychotic drugs are also useful in treatment of organic, affective, and drug-induced psychosis, suggesting that dopamine disturbances are not unique to schizophrenia.

Pathophysiologic

Pathophysiological evidence for schizophrenia as a discrete disease has come from studies showing decreased frontal lobe regional blood flow[23,24] and lower glucose utilization in the frontal cortex and left central gray matter in schizophrenics when compared with controls.[25] The latter study supports the hypothesis of left hemispheric deficits in schizophrenia, as does a study showing increased frequency of left-handedness and mixed-handedness among schizophrenic patients compared with controls.[26] Flor-Henry's study[27] demonstrated an increased risk of schizophrenic-like psychosis in patients with left temporal lobe epilepsy, whereas affective illness often developed in patients with right temporal lobe damage.

Anatomic

Recent studies utilizing computed tomography (CT) scans and pneumoencephalograms have

shown subtle manifestations of brain atrophy including ventricular enlargement and dilatation of cortical sulci in a subgroup of chronic schizophrenics.[28,29] This subgroup of schizophrenics has been noted in subsequent controlled studies to have histories of poorer premorbid adjustment,[30] greater neuropsychiatric deficits,[31] poorer reponse to neuroleptic drugs,[32] more nonfocal neurological signs,[33] more impaired smooth pursuit eye movements,[34] a different distribution of neuroanatomical asymmetries seen on CT scans,[34] a different frequency of leukocyte antigen (HLA) A2,[35] and higher whole blood serotonin concentration.[36] Another similar study demonstrated that this subgroup of schizophrenic patients had a preponderance of "negative" symptoms of schizophrenia (affective flattening, avolition, anhedonia, alogia, apathy), while those with small ventricles were characterized by "positive" symptoms (delusions, hallucinations, positive formal thought disorder, bizarre behavior).[37]

The above studies suggest a new model for the etiology of schizophrenia.[37,38] According to this model there is *negative,* or *defect, schizophrenia* characterized by diffuse brain abnormalities (principally atrophic), impaired cognitive function as measured by tests of the sensorium, and a clinical picture in which negative symptoms predominate. This negative, or defect, schizophrenia represents a syndrome that is similar in some respects to the dementias. The nature of the neuropathological process is uncertain; these factors may include an inherited predisposition, infectious processes, or environmental insults such as poor nutrition or hygiene. On the other hand, *positive schizophrenia* is hypothesized to be a "release" phenomenon due to a more focal brain dysfunction, possibly primarily neurochemical, and is characterized by normal neuropsychological testing and a preponderance of positive symptoms. These two types of schizophrenia may also differ in terms of outcome and response to treatment, with negative schizophrenia leading to a more severe illness with a more chronic, deteriorating course and a poorer response to treatment.

Environmental

Although the above observations indicate that genetic and biological factors are important in schizophrenia, they do not exclude the operation of environmental factors on a genetically transmitted predisposition to schizophrenia, as indicated by the 50 percent discordance for schizophrenia in monozygotic twins. An interesting recent study revealed that offspring of schizophrenic mothers who were later diagnosed as schizophrenic had a higher incidence of perinatal complications than did offspring who did not develop the illness.[39] Thus, birth complications resulting in neurologic damage may in susceptible individuals cause schizophrenia. Although the nature of other environmental factors has not been firmly established, stressful life events seem to be one important variable. Brown and Birley[40] have shown that in the three-week period prior to symptom onset, hospitalized schizophrenic patients had a life-event rate that was three times that of controls. They have also shown that 60 percent of relapses seem directly related to severe life stress.[40] Jacobs and Meyers[41] noted that first-admission schizophrenics demonstrate 50 percent more life events for the year preceding symptom onset than population controls. Moreover, the studies of Vaughn and Leff[42] have shown that in living situations (home or institution) characterized by low levels of expressed emotion, relapse rates are low regardless of medical treatment, whereas in environments with high levels of expressed emotion, relapse rates are high despite pharmacologic treatment.

Geographic mobility also is an important factor in the incidence of schizophrenia.[43,44] In general, the more extreme the change, the more pronounced the effect will be. Transition from one culture or country to another is more important than the mere distance traveled.

Over 50 studies in many countries have consistently shown a clustering of schizophrenia in the lower classes of urban populations.[45] Detailed analysis of the rates of intergenerational occupational morbidity of schizophrenics makes it seem highly unlikely that class differences in the etiology of schizophrenia result entirely from downward drift. Faris[46] hypothesized that the high degrees of social isolation and disintegration inherent in lower-class urban life are powerful causal factors in schizophrenia.

Lidz and colleagues[47] postulated the premorbid influence of specific styles of parenting, and Bateson et al[48] coined the term *double bind* to describe a special form of ambivalence in which mother,

Continued on page 114

Continued from page 112

father, or siblings make overt requests or imply demands for a strong reaction that conflicts with the one required by the situation (such as complaining to the child that he never is physically affectionate while the parent always cringes at an attempted embrace). The problem with most of these interpretations of family patterns is that it is equally likely that they could be secondary to family problems created by an ill child.

Course

The course of schizophrenia is highly variable, but recurrent episodes of active psychosis and permanent impairment are most common.[49] The active and residual phases are in general characterized by different groups of symptoms. The first group consists of the more flagrant, dramatic symptoms associated with an active phase of the psychosis (ie, auditory hallucinations, florid delusions, loose associations and complaints of thought insertion, thought broadcasting, thoughts of being controlled, and thought withdrawal). The second group of characteristic symptoms occurs during the residual phase but may appear during the initial prodromal stage of the illness. These symptoms are characterized by apathy, lack of ambition, flattened or blunted affect, impoverished thought, social withdrawal, and poor self-care.

Complications

The life expectancy of patients with schizophrenia is lower than that of the general population because of the increased rate of suicide and death from a variety of medical conditions.[3] The medical complications result in part from institutional care (illnesses such as hepatitis); however, they also probably result from economically deprived environments (in which individuals with these disorders often live) and from poor self-care and medical preventive care. As a result studies have shown that patients with chronic mental illness have two to four times the number of medical diagnoses that other patients have.[50,51]

Prognosis has improved with the advent of phenothiazines and other antipsychotic agents, but these medications are most effective against the active phase symptoms and least effective against the more chronic residual symptoms.[52] Full recovery is uncommon and usually occurs in the first two years; after five years few patients recover. There is a distinct spectrum of severity, with many patients able to function vocationally and socially on small dosages of medication, whereas other patients, despite large dosages of antipsychotics, have frequent acute psychotic episodes with downward drift in their socioeconomic status and profound social withdrawal. Surprisingly, World Health Organization studies demonstrate that outcome for schizophrenia is better in less developed societies, suggesting that social stress and support may well be important influences on outcome.[53]

Social recovery, defined as the ability to live outside the hospital, is also variable. For many patients, supervised housing (halfway houses, nursing homes) is essential, whereas others live with families or on their own and manage well. The economic consequences are staggering, with an estimated $14 billion annual loss in individual productivity.[22] The cost of health and social services, as well as personal and family suffering, is incalculable.

Treatment

There is little question that the antipsychotic drugs are effective in treating the symptoms of schizophrenia.[52] These drugs help most patients to a substantial degree but do not provide a cure for the disease in that the majority of patients require maintenance treatment. An example of the dramatic efficacy of antipsychotic drugs is shown by the data from the National Institute of Mental Health (NIMH) Collaborative Study No. 1.[54] Approximately 50 percent of the control group became worse despite the psychologic effect provided by placebo. This deterioration was so profound that many patients were withdrawn from the study. In contrast approximately 75 percent of the patients on antipsychotic medication improved, although a few were helped only minimally. This study has been verified by literally hundreds of double-blind studies that consistently show a good antipsychotic effect of neuroleptics.[52]

Controlled studies have shown that all phenothiazines, as well as the newer antipsychotics (butyrophenones, thioxanthenes, dihydroindolones, dibenzoxazepines), are clearly superior to placebo and equal in therapeutic efficacy when

Continued on page 117

Continued from page 114

used in equivalent dosages.[11] Studies have shown that all types of schizophrenics have been found to respond equally well to each of the effective antipsychotics; nonetheless, it is also clinically apparent that occasionally a patient refractory to one antipsychotic can exhibit a good response to another. The clinician should choose one drug, find the optimal dosage for the patient, and maintain the dose level for sufficient time for the drug to exert its behavioral effect. Only after several days to weeks in the severely agitated patient or several weeks to months in the less disturbed patient should the drugs be changed. Because of differences in metabolism, absorption, and accumulation or binding at receptor sites, there may be marked differences in efficacy in the individual patient.[11] For instance Curry et al[55] found wide individual differences in the blood levels of patients taking identical dosages of the same antipsychotic.

The therapeutic alliance with the physician is an integral aspect of treatment. A strong alliance will enhance adherence to medication regimens, allow the physician to diagnose early signs of exacerbation of illness, and aid the physician in providing the family with information about etiology, rationale for the use of medications, and a prognosis, as would happen with any other chronic illness. The importance of this therapeutic relationship was demonstrated by the finding by Gunderson and co-workers[56] that 50 percent of institutionalized schizophrenic patients freed from active symptoms by the use of drugs discontinued medication after discharge because the lack of continuing therapeutic contact made them feel uncared for. Primary care physicians must monitor schizophrenic patients carefully for adherence because noncompliance has been found to be the statistical norm in many studies.

Prophylactic Effect of Antipsychotics

Davis[52] reviewed 24 controlled studies comparing the incidence of relapse on placebo with that on maintenance antipsychotics. These studies were carried out in a variety of settings in England and the United States. In every study more patients relapsed with placebo than with drugs.

It is also evident that some patients do not relapse even if their drugs are discontinued. Since long-term toxicity does exist (tardive dyskinesia), it is desirable to treat only those patients who need to be taking drugs and to discontinue medications in those who do not. The NIMH Collaborative Study Group found that patients who need relatively high doses of drugs had a greater frequency of relapse, whereas patients who had been hospitalized 15 years or more and were maintained on small token dosages rarely relapsed. The former group deserve maintenance medication, whereas in the latter drug-free trials should be instituted. Every effort should be made in both inpatient and outpatient management to treat the patient with the most minimal drug dosage required for management, since drug side effects are significant. A history of relapses when the drug dosage is lowered or discontinued is obviously another indication for long-term medication.

Side Effects

The antipsychotic drugs produce a wide variety of side effects (Table 5). The most common are the extrapyramidal disturbances, including acute dystonic reactions, akathisia, akinesia, and pseudoparkinsonism, which are secondary to the antidopaminergic action of antipsychotics on the striopalidol area of the brain.[57] These disturbances appear early in treatment and are more likely to occur with the more potent neuroleptic agents that have high dopamine blocker activity and little anticholinergic effect. The addition of anticholinergic agents usually alleviates these side effects; another alternative is to change to a class of antipsychotics that are less potent dopamine blockers and have more anticholinergic effects.[58] It has been shown that tolerance to the extrapyramidal side effects seems to develop, and the antiparkinsonian drugs can often be discontinued after one or two months without re-exacerbation of extrapyramidal symptoms.[58]

Tardive dyskinesia, characterized by involuntary dyskinetic movements, especially of the buccolingual masticatory muscles, is a more serious side effect of the antipsychotic agents.[59] It is hypothesized to be associated with dopamine receptor hypersensitivity in the basal ganglia.[60] A recent review of 56 studies yielded an average prevalence of 20 percent in neuroleptic-treated patients compared with 5 percent of "spontaneous" dyskinesia in 19 studies of untreated individuals.[59] Advancing age and female sex were the only two variables consistently found to be associated with preva-

Table 4. Organic Diseases Presenting Psychiatric Syndromes

Organic Disease	Prevalence (Sex and Age)	Common Medical Symptoms	Psychiatric Symptoms and Complaints	Impaired Performance and Behavior	Diagnostic Pitfalls
Hyperthyroidism (thyrotoxicosis)	Female 3:1 30-50 yr	Tremor, sweating, loss of weight and strength	Anxiety if rapid onset; depression if slow-onset mania	Occasional hyperactive or grandiose behavior	Long lead time; rapid onset resembles anxiety attack
Hypothyroidism (myxedema)	Female 5:1 30-50 yr	Puffy face, dry skin, cold intolerance	Anxiety with irritability; thought disorder (somatic delusions, hallucinations)	Myxedema madness (delusional, paranoid, and belligerent behavior)	Myxedema madness may mimic schizophrenia; mental status is clear even during most disturbed behavior
Hyperparathyroidism	Female 3:1 40-60 yr	Weakness, anorexia, fractures, calculi, peptic ulcer	Either state may cause anxiety (hyperactivity and irritability) or depression (apathy and withdrawal)	Either state may proceed to toxic psychosis (confusion, disorientation, clouded sensorium)	Anorexia and fatigue of slow-growing adenoma resemble involutional depression
Hypoparathyroidism	Female 40-60 yr	Hyperreflexia, spasms, tetany			May follow thyroidectomy
Hyperadrenalism (Cushing's disease)	Both sexes Adults	Weight gain, fat alteration, easy fatigability	Varied (depression, anxiety, thought disorder with somatic delusions)	Rarely causes behavioral abnormality	Bizarre somatic delusions caused by bodily changes resemble schizophrenia
Adrenocortical insufficiency (Addison's disease)	Both sexes Adults	Weight loss, hypotension, skin pigmentation	Depression (negativism, apathy); thought disorder (suspiciousness)	Toxic psychosis with confusion and agitation	Long lead time; weight loss, apathy, and despondency resemble depression
Porphyria, acute intermittent	Female 20-40 yr	Abdominal crises, paresthesias, weakness	Anxiety, severe with rapid onset; mood swings	Extremes of excitement or withdrawal; emotional or angry outbursts	Often truly neurotic lifestyle, crises resemble conversion reactions or anxiety attacks
Pernicious anemia	Female 40-60 yr	Weight loss, weakness, glossitis, neuritis of extremities	Depression (feelings of guilt and worthlessness)	Eventual brain damage with confusion and memory loss	Gradual onset, sometimes many months; easily mistaken for involutional depression; normal early blood studies may give false reassurance

Hepalolenticular degeneration (Wilson's disease)	Male 2:1 Adolescents	Liver and extrapyramidal symptoms, Kayser-Fleischer rings	Mood swings, sudden and changeable; anger, explosive	Eventual brain damage with memory and IQ loss; combativeness	In late teens may resemble "adolescent storm" incorrigibility or schizophrenia
Hypoglycemia	Both sexes Adults	Tremor, sweating, hunger, fatigue, dizziness	Anxiety (fear and dread); depression with fatigue	Agitation, confusion; eventual brain damage	Can mimic anxiety attack or acute alcoholism; bizarre behavior may draw attention away from somatic symptom
Intracranial tumor	Both sexes Adults	None early; headache, vomiting, papilledema later	Varied (depression anxiety, personality changes)	Loss of memory, judgment; self-criticism; clouding of consciousness	Tumor location may not determine early symptoms
Pancreatic carcinoma	Male 3:1 50-70 yr	Weight loss, abdominal pain, weakness, jaundice	Depression (sense of imminent doom but without severe guilt)	Peculiar loss of drive and motivation	Insidious onset; same age range and symptoms as those of involutional depression
Pheochromocytoma	Both sexes Adults	Headache, sweating during elevated blood pressure	Anxiety (panic, fear, apprehension, trembling)	Inability to function during an attack	Classic symptoms of anxiety attack; intermittently normal blood pressure may discourage further studies
Multiple sclerosis	Female 20-45 yr	Motor and sensory loss, scanning speech, nystagmus	Varied (personality changes, mood swings, depression); "bland euphoria" uncommon	Inappropriate behavior for patient owing to subtle personality changes	Marked variability of symptoms over long period of time; early neurologic symptoms mimic hysteria or conversion reactions
Systemic lupus erythematosus	Female 8:1 20-40 yr	Multiple symptoms of cardiovascular, genitourinary, gastrointestinal, and other systems	Varied (thought disorder, depression, confusion)	Toxic psychosis unrelated to steroid treatment	Long lead time, perhaps many years; psychiatric picture variable over time; thought disorder resembles schizophrenia

Source: Peterson HW, Martin MJ[13]

Table 5. Antipsychotic Drugs

Drug Category	Generic	Trade Name	Sedation	Extra-pyramidal Effects*	Potency (mg)	Hyper-tension	Anti-emetic	Inhibition of Ejaculation	Cholestatic Jaundice	Photo-sensitivity	Aplastic Anemia
Dimethyl-aminopropyl phenothiazine (aliphatic) derivatives	Chlorpromazine	Thorazine	Strong	Type II Moderate	Low	Moderate to strong	Moderate	Weak	Strong	Strong	"Strong" (rare effect)
	Promazine	Sparine									
	Promethazine	Phenergan									
		Remsed									
Dimethyl-aminopropyl thioxanthene derivative	Chlorprothixene	Taractan									
Piperadine derivatives	Mesoridazine	Senentil	Moderate	Uncommon	Low	Moderate	Weak	Strong	Low	Low	Low
	Piperacetazine	Quide									
	Thioridazine	Mellaril									
Piperazine derivatives	Acetophenazine	Tindal	Weak	Strong Types I and II	Strong	Weak	Strong	Weak	Low	Low	Low
	Fluphenazine	Permitil									
		Prolixin									
	Perphenazine	Trilafon									
	Trifluoperazine	Stelazine									
Butyrphenones	Haloperidol	Haldol									
	Droperidol	Inapsine									
Thioxanthenes piperazine type	Thiothixene	Navane									
Hydroindolone	Molindone	Moban									

*Extrapyramidal reactions:
Type I: Acute dystonic reaction characterized by prolonged abnormal tonic contraction of muscle groups, especially those of the head, neck, or extraocular muscles (oculogyric crisis)
Type II: Pseudoparkinsonism characterized by akinesia (muscle fatigue and weakness), rigidity, alternating resting tremor, and autonomic nervous sytem dysfunction (drooling, hyperhidrosis, and heat intolerance)
Akathisia: Subjective desire to be in constant motion; associated with inability to sit still, hyperactivity, continuous agitation, restless movements, rocking and shifting of weight while standing, tapping of the feet while sitting

Continued on page 123

Continued from page 120

lence. As a result of the risk of tardive dyskinesia, schizophrenic patients should be maintained on the lowest possible dosages of antipsychotic drugs. The earliest signs of tardive dyskinesia are fine vermicular movements of the tongue, presence of tics in the facial area, and abnormal jaw movements.[61] Once tardive dyskinesia is diagnosed, most clinicians agree that antipsychotics should be stopped. If this is done soon after the development of the dyskinesia, remission within six weeks is common,[62] although many patients already have irreversible dyskinesia at the time of initial diagnosis. Should removal of the antipsychotic because of tardive dyskinesia lead to exacerbation of psychotic symptoms, the clinician and patient are faced with a difficult choice, weighing the social and physical ramifications of this disfiguring disorder against the risk of relapse into active psychosis. In many cases the patient must be maintained on antipsychotics despite the evidence of tardive dyskinesia, but a written record of informed consent is advised so that the patient is aware that the condition may be irreversible if treatment is continued.[63]

Conclusions

It is essential for family physicians to become familiar with the modern "narrow" criteria for schizophrenia in order to re-evaluate diagnosis in patients who became ill prior to the change in diagnosis formulated by the DSM III. Phenomenology, course, family history, presence of affective symptoms or organicity, social and vocational history, and response to pharmacologic treatment are all important parameters in diagnosis.

Schizophrenia is probably a final common pathway for several different etiologic mechanisms (factors include genetic endowment, perinatal trauma, neurological injury, stressful life conditions), and its course and response to treatment are variable. However, it is generally an illness with a chronic course, necessitating long-term pharmacologic treatment that itself carries a risk for irreversible tardive dyskinesia. Because of the chronicity of the illness and hazards associated with long-term treatment, a close therapeutic alliance with family and patient may markedly improve the course by enhancing patient compliance with medications, helping the patient find a stable environment in which to live, and providing support and education to the family in managing an illness that often alienates the patient from necessary social supports.

Finally, schizophrenia research seems to be at a stage similar to that of research on affective disorder ten years ago. There has been an exponential increase in studies of the genetics, biochemistry, family pathology, association with stress, and phenomenology of this devastating illness. Promising neuropsychiatric research has isolated a subgroup of schizophrenics who appear to have subtle indices of neurological damage and a different course and prognosis. Unfortunately, treatment is still symptomatic, not curative, but studies of neurotransmitters like γ-aminobutyric acid, dopamine, serotonin, and acetylcholine and the development of medications that are "pure" (selectively affecting one neurotransmitter) hold the promise of improvements in future pharmacotherapy.

References

1. Kendel RE, Cooper JE, Gourlay AJ, Copeland JRM: Diagnostic criteria of American and British psychiatrists. Arch Gen Psychiatry 25:123, 1971
2. Katz M, Cole JO, Lowery HA: Studies of the diagnostic process: The influence of symptom perception, past experience, and ethnic background on diagnostic decisions. Am J Psychiatry 125:937, 1969
3. Diagnostic and Statistical Manual of Mental Disorder (DSM III), ed 3. Washington, DC, American Psychiatric Association, 1980
4. Pope HG Jr, Lipinski JF Jr: Diagnosis in schizophrenia and manic depressive illness, a reassessment of the specificity of "schizophrenic" symptoms in the light of current research. Arch Gen Psychiatry 35:811, 1978
5. Taylor MA, Gaztanaga P, Abrams R: Manic-depressive illness and acute schizophrenia: A clinical, family history and treatment-response study. Am J Psychiatry 131: 678, 1974
6. Feighner JP, Robins E, Guze SB, et al: Diagnostic criteria for use in psychiatric research. Arch Gen Psychiatry 26:57, 1972
7. Taylor MA, Abrams R: The prevalence of schizophrenia: A reassessment using modern diagnostic criteria. Am J Psychiatry 135:945, 1978
8. Ries R, Bokan J, Schuckit M: Modern diagnosis schizophrenia in hospitalized psychiatric patients. Am J Psychiatry 137:1419, 1980
9. Morrison J, Clancy J, Crowe R, Winokur G: The Iowa 500: I. Diagnostic validity in mania, depression and schizophrenia. Arch Gen Psychiatry 27:457, 1972
10. Day M, Semrad EV: Schizophrenic reactions. In Nicholi Am (ed): The Harvard Guide to Modern Psychiatry. Cambridge, Mass, The Belknap Press of the Harvard University Press, 1978, p 207
11. Klein DF, Gittelman R, Quitkin F, Rifken A: Diagnosis and Drug Treatment of Psychiatric Disorders: Adults and Children, ed 2. Baltimore, Williams & Wilkins, 1981, p 59
12. Rabins PV, Folstein MF: Delirium and dementia: Diagnostic criteria and fatality rates. Br J Psychiatry 140:149, 1982

13. Peterson HW Jr, Martin MJ: Organic disease presenting as a psychiatric syndrome. Postgrad Med 54:78, 1973

14. Drugs that cause psychiatric symptoms. Med Lett 23:9, 1981

15. Tsuang MT, Simpson JC, Kronfol Z: Subtypes of drug abuse with psychosis: Demographic characteristics, clinical features and family history. Arch Gen Psychiatry 39: 141, 1982

16. Freedman AM, Kaplan HI, Sadock BJ: Modern Synopsis of Comprehensive Textbook of Psychiatry II. Baltimore, Williams & Wilkins, 1976, pp 211-212

17. Tsuang MT, Vandermey R: Genes and the Mind: Inheritance of Mental Illness. New York, Oxford University Press, 1980

18. Gottesman II, Shields J: Contributions of twin studies to perspectives in schizophrenia. In Maher BA (ed): Progress in Experimental Personality Research. New York, Academic Press, 1966, vol 3, pp 1-84

19. Fischer M, Harvald B, Hague M: A Danish twin study of schizophrenia. Br J Psychiatry 115:981, 1969

20. Kety S: Recent genetic and biochemical approaches to schizophrenia. In Simpson LL (ed): Drug Treatment of Mental Disorders. New York, Raven Press, 1976, pp 1-11

21. Greenblatt DJ, Shader R: Rational use of psychotropic drugs: III. Major tranquilizers. Am J Hosp Pharm 31: 1226, 1974

22. Manschreck TC: Current concepts in psychiatry: Schizophrenic disorders. N Engl J Med 305:1628, 1981

23. Ingvar DH, Franzen G: Abnormalities of cerebral blood flow distribution in patients with chronic schizophrenia. Acta Psychiatr Scand 50:425, 1974

24. Franon G, Ingvar DH: Abnormal distribution of cerebral activity in chronic schizophrenia. J Psychiatr Res 12: 199, 1975

25. Buchsbaum MS, Ingvar DH, Kessler R, et al: Cerebral glucography with positron tomography: Use in normal subjects and in patients with schizophrenia. Arch Gen Psychiatry 39:251, 1982

26. Nasrallah HA, Keelor IS, Van Schroeder C, Whitters MM: Motor lateralization in schizophrenic males. Am J Psychiatry 138:1114, 1981

27. Flor-Henry P: Psychosis and temporal lobe epilepsy. Epilepsia 10:363, 1969

28. Golden CJ, Moses JA, Zelazowski R, et al: Cerebral ventricular size and neuropsychological impairment in young chronic schizophrenics. Arch Gen Psychiatry 37:619, 1980

29. Andreasen NC, Smith MR, Jacob CG, et al: Ventricular enlargement in schizophrenia: Definition and prevalence. Am J Psychiatry 139:292, 1982

30. Weinberger DR, Cannon-Spoor E, Potkin SG, Wyatt RJ: Poor premorbid adjustment CT scan abnormalities in chronic schizophrenia. Am J Psychiatry 137:1410, 1980

31. Dobnely EF, Weinberger DR, Waldman IN, et al: Neuropsychological prediction of structural brain abnormalities on computed tomography in a group of chronic schizophrenic patients. J Nerv Ment Dis 168:305, 1980

32. Weinberger DR, Bigelow LB, Kleinman JE, et al: Cerebral ventricular enlargement in chronic schizophrenia: Association with poor response to treatment. Arch Gen Psychiatry 37:11, 1980

33. Weinberger DR, Rorrey EF, Neophytides AN, et al: Lateral cerebral ventricular enlargement in chronic schizophrenia. Arch Gen Psychiatry 36:735, 1979

34. Luchins DJ, Weinberger DR, Wyatt RJ: Schizophrenia: Evidence for a subgroup with reversed cerebral asymmetry. Arch Gen Psychiatry 36:1309, 1979

35. Luchins DJ, Rorrey EF, Weinberger DR, et al: HLA-antigens in schizophrenia: Differences between patients with and without evidence of brain atrophy. Br J Psychiatry 136:245, 1980

36. Delis LF, Neckens LM, Weinberger DR, et al: Increased whole blood serotonin concentrations in chronic schizophrenic patients. Arch Gen Psychiatry, in press

37. Andreasen NC, Olson SA, Dennert JW, Smith MR: Ventricular enlargement in schizophrenia: Relationship to positive and negative symptoms. Am J Psychiatry 139:297, 1982

38. Crow TJ: Molecular pathology of schizophrenia: More than one disease process. Br Med J 284:1, 1980

39. Parnas J, Schulsinger F, Teasdale TW, et al: Perinatal complications and clinical outcome within the schizophrenia spectrum. Br J Psychiatry 140:416, 1982

40. Brown GW, Birley JLT: Crisis and life change on the onset of schizophrenia. J Health Soc Behav 9:203, 1968

41. Jacobs S, Meyers JK: Recent life events and acute schizophrenic psychosis: A controlled study. J Nerv Ment Dis 162:75, 1976

42. Vaughn CE, Leff JF: The influence of the family and social factors on the course of psychiatric illness: A comparison of schizophrenic and depressed neurotic patients. Br J Psychiatry 129:125, 1976

43. Astrup C, Odegard O: Internal migration and disease in Norway. Psychiatry Q (suppl):34, 116, 1960

44. Cade JF, Krupinski F: Incidence of psychiatric disorders in Victoria in relation to country of birth. Med J Aust 49:400, 1962

45. Kohn ML: The interaction of social class and other factors in the etiology of schizophrenia. Am J Psychiatry 133:177, 1976

46. Faris REL: Social Disorganization. New York, Ronald Press, 1955

47. Lidz T, Fleck S, Correlison AR: Schizophrenia and the Family. New York, International Universities Press, 1965

48. Bateson G, Jackson DD, Haley J, Weakland J: Toward a theory of schizophrenia. Behav Sci 1:251, 1956

49. Hamilton M (ed): Fish's Schizophrenia, ed 2. Bristol, England, John Wright, 1976

50. Hankin J, Oktay JS: Mental Disorder and Primary Care: An Analytic Review of the Literature. Alcohol, Drug Abuse, and Mental Health Administration (Rockville, Md). DHEW publication No. (ADM) 78-661, Government Printing Office, 1979

51. Hoeper EW, Nycz GR, Regier DA, et al: Diagnosis of mental disorder in adults and increased use of health services in four outpatient settings. Am J Psychiatry 137:207, 1980

52. Davis J: Recent developments in the treatment of schizophrenia. Psychiatr Ann 6:71, 1976

53. Strauss JS, Carpenter JW Jr: The prediction of outcome in schizophrenia: II. Relationships between predictor and outcome variables: A report of the WHO International Pilot Study of Schizophrenia. Arch Gen Psychiatry 31:37, 1974

54. Cole JR, Goldberg SC, Davis JM: Drugs in the treatment of psychosis: Controlled studies. In Solomon P (ed): Psychiatric Drugs. New York, Grune & Stratton, 1966, pp 153-180

55. Curry SH, Marsh JHL, Davis JM, Janowsky DS: Chlorpromazine plasma levels and effects. Arch Gen Psychiatry 22:289, 1970

56. Gunderson JG, Autry JH, Mosher LR, Buchsbaum S: Special report: Schizophrenia. Schizophrenia Bull 9:15, 1973

57. Chase TN: Drug-induced extrapyramidal disorders: Neurotransmitters. Res Publ Assoc Nerv Ment Dis 50:448, 1972

58. Donlon DT, Stenson RL: Neuroleptic induced extrapyramidal symptoms. Dis Nerv System 37:625, 1976

59. Kane JM, Smith JM: Tardive dyskinesia: Prevalence and risk factors, 1959 to 1979. Arch Gen Psychiatry 39:473, 1982

60. Klawan HL Jr: The pharmacology of tardive dyskinesias. Am J Psychiatry 130:82, 1973

61. American College of Neuropsychopharmacology—Food and Drug Administration Task Force: Drug therapy: Neurological syndromes associated with antipsychotic drug use. N Engl J Med 289:20, 1973

62. Quitkin R, Rifkin A, Gochfled L, Klein DF: Tardive dyskinesia: Are the first signs reversible? Am J Psychiatry 134:84, 1977

63. Ayd FJ: Ethical and legal dilemmas posed by tardive dyskinesia. Int Drug Ther Newsletter 12:29, 1977