Chapter 2

Background Information

Schizophrenia

History

The history of psychiatrists and neurologists who have written and theorized about schizophrenia parallels the history of psychiatry itself. The magnitude of the clinical problem has consistently attracted the attention of major figures throughout the history of the discipline.

Emil Kraepelin (1856-1926), German psychiatrist, adapted Morel's term (1852) "*demence precoce*" to "*dementia precox*," a term that emphasized a distinct cognitive process (dementia) and the early onset (precox) that is characteristic of the disorder. Kraepelin further distinguished patients with dementia precox from those he classified as being afflicted with manic-depressive psychosis or paranoia. Patients with dementia precox were characterized as having long-term deteriorating course and common clinical symptoms of hallucinations and delusions. Kraepelin's views regarding the course of schizophrenia are sometimes misrepresented in terms of the certainty of a deteriorating course, since he did acknowledge that about 4 percent of his patients had complete recoveries and 13 percent had significant remissions. Patients with manic-depressive psychosis were differentiated from patients with dementia precox by the presence of distinct episodes of illness that were separated be periods of normal functioning. Patients with paranoia had persistent persecutory delusions as their major symptom but did not have the deteriorating course of dementia precox or the intermittent symptoms of manic depressive psychosis.

EMIL KRAEPELIN CRITERIA

1. Disturbances of attention and comprehension
2. Hallucinations, especially auditory (voices)
3. Gedankenlautwerden (audible thoughts)
4. Experiences of influenced thought
5. Disturbances in the flow of thought, above all a loosening of associations
6. Impairment of cognitive function and judgement
7. Affective flattening
8. Appearance of morbid behavior
    - Reduced drive
    - Automatic obedience
    - Echolalia, echopraxia
    - Acting out
    - Catatonic frenzy
    - Stereotypy
    - Negativism
    - Autism
    - Disturbance of verbal expression

Eugen Bleuler (1857-1939) gave the term " *schizophrenia*," and the term replaced "dementia precox" in the literature. Bleuler conceptualized the term to signify the presence of a schism between thought, emotion, and behavior in affected patients. However, the term is widely misunderstood, especially by the lay public, as signifying a split personality. Split personality (now called dissociative identity disorder is an entirely different disorder that is categorized in the fourth edition of Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) with the other dissociative disorders). A major distinction that Bleuler drew between his concept of schizophrenia and Kraepelin's concept of dementia precox was that a deteriorating course is not necessary in the concept of schizophrenia, as it was in dementia precox. To explain further his theory regarding the internal mental schisms of

affected patients, Bleuler described specific *fundamental (or primary) symptoms* of schizophrenia, including a thought disorder characterized by association disturbances, particularly looseness. Other fundamental symptoms were affective disturbances, autism, and ambivalence. Bleuler also described accessory (secondary) symptoms, which had been a prominent part of Kraepelin's conceptualization of the disorder.

EUGEN BLEULER CRITERIA

Primary symptoms (The four As.) : 1. associations
2. affect
3. autism
4. ambivalence

Secondary symptoms : 1. hallucination
2. delusion

Gabriel Langfeldt divided the patients with major psychotic symptoms into two groups, those with true schizophrenia and those with schizophreniform psychosis. Langfeldt emphasized the importance of depersonalization, autism, emotional blunting, an insidious onset, and feelings of derealization in his description of true schizophrenia. True schizophrenia also came to be known as nuclear schizophrenia, literature that followed Langfeldt's papers.

GABRIEL LANGFELDT CRITERIA

1. Symptom criteria :

Significant clues to a diagnosis of schizophrenia are (if no sign of cognitive impairment, infection, or intoxication can be demonstrated)

a. Changes in personality, which manifest themselves as a special type of emotional blunting followed by lack of initiative, and altered, frequently peculiar behavior

b. In catatonic types, the history and the typical signs in periods of restlessness and stupor. (with negativism, oily facies, catalepsy, special vegetative symptoms, etc.)

c. In paranoid psychoses, essential symptoms of split personality (or depersonalization symptoms) and a loss of reality feeling (derealization symptoms) or primary delusions

d. Chronic hallucinations

2. Course criterion :

A final decision about diagnosis cannot be made before a follow-up period of at least five years has shown a long-term course of disease.

Kurt Schneider described a number of *first-rank symptoms* that he considered in no way specific for schizophrenia but of pragmatic value in making a diagnosis. Schizophrenia, Schneider pointed out, can also be diagnosed exclusively on the basis of *second-rank symptoms* and an otherwise typical clinical appearance. Schneider did not mean those symptoms to be applied rigidly. He warned the clinician that the diagnosis of schizophrenia should be made in certain patients who failed to show first-rank symptoms. Unfortunately, that warning is frequently ignored, and the absence of such symptoms in a single interview is sometimes taken as evidence that the person does not have schizophrenia.

KURT SCHNEIDER CRITERIA

1. First-rank symptoms :
    a. Audible thoughts
    b. Voices arguing or discussing or both
    c. Voices commenting
    d. Somatic passivity experiences
    e. Thought withdrawal and other experiences of influenced thought
    f. Thought broadcasting
    g. Delusional perceptions
    h. All other experiences involving volition, made affects, and made impulse
2. Second-rank symptoms :
    a. Other disorders of perception
    b. Sudden delusional ideas
    c. Perplexity
    d. Depressive and euphoric mood changes
    e. Feelings of emotional impoverishment
    f. And several others...

Karl Jaspers was a psychiatrist and a philosopher, and he was a major contributor to existential psychoanalysis. Jaspers approached psychopathology with the idea that there are no firm conceptual frameworks or fundamental principles. In his theories regarding schizophrenia, therefore, Jaspers attempted to remain unencumbered by traditional concepts, such as subject and object, cause and effect, and reality and fantasy. One specific development of that philosophy was his interest in the content of psychiatric patients' delusions.[27]

Epidemiology

In the United States the lifetime prevalence of schizophrenia has been variously reported as ranging from 1 to 1.5 percent; consistent with that range, the National Institute of Mental Health (NIMH) sponsored Epidemiologic Catchment Area (ECA) study reported a lifetime prevalence of 1.3 percent. About 0.025 to 0.05 percent of the total population are treated for schizophrenia in any one year. Although two thirds of those treated patients require hospitalization, only about half of all schizophrenic patients obtain treatment, in spite of the severity of the disorder.

Age and Sex : Schizophrenia is equally prevalent in men and women. However, the two sexes show several differences in the onset and the course of illness. Men have an earlier onset of schizophrenia than do women. More than half of all male schizophrenic patients but only a third of all female schizophrenic patients have their first psychiatric hospital admission before age 25. The peak ages of onset for men are 15 to 25; for women the peak ages are 25 to 35. The onset of schizophrenia before age 10 or after age 55 years old. Some studies have indicated that men are more likely than are women to be impaired by negative symptoms and that women are more likely to have better social functioning than men. In general, the outcome for female schizophrenic patients is better than the outcome for male schizophrenic patients.

Seasonality of Birth : A robust finding in schizophrenia research is that persons who later have schizophrenia are more likely to have been born in the winter and early spring and less likely to have been born in late spring and summer. Specifically, in the northern hemisphere, including the United States, schizophrenic persons were more often born in the months from January to April. In the southern hemisphere, schizophrenic persons were more often born in the months from July to September. Various hypotheses to explain that observation have been put forward. They include the hypothesis that some season-specific risk factor is operative, such as a virus or a seasonal change in diet. Another hypothesis is that persons who have the genetic predisposition for schizophrenia have an increased biological advantage to survive season-specific insults.

Medical Illness : Schizophrenic persons have a higher mortality rate from accidents and natural causes than do the general population. That increase in mortality is not explained by institution-related variables. The higher rate may be related to the fact that the diagnosis and the treatment of medical and surgical conditions in schizophrenic patients can be a clinical challenge. Several studies have found that up to 80 percent of all schizophrenic patients have significant concurrent medical illnesses and that up to 50 percent of those conditions may be undiagnosed.

Suicide : Suicide is a common cause of death among schizophrenic patients, partly because clinicians still tend to associate suicide more with mood disorders that with the psychotic disorders. About 50 percent of all patients with schizophrenia attempt suicide at least once in their lifetimes, and 10 to 15 percent of schizophrenic patients die by suicide during a 20 year follow-up period. Male and female schizophrenic patients are equally likely to commit suicide. The major risk factors for suicide among schizophrenic persons include the presence of depressive symptoms, young age, and high levels of premorbid functioning (especially a college education). That group may realize the devastating significance of their illness more than do other groups of schizophrenic patients and may see suicide as a reasonable alternative. Treatment approaches to such patients may included pharmacological treatment of the depression, addressing issues of

loss in psychotherapy , and the use of support groups to help direct the patient's ambitions toward some obtainable goal.

Population Density : The prevalence of schizophrenia has been correlated with local population density in cities with populations of more than 1 million people. That correlation is weaker in cities of 100,000 to 500,000 people and is not present in cities with fewer than 10,000 people. The effect of population density is consistent with the observation that the incidence of schizophrenia in children of either one or two schizophrenic parents is twice as high in cities as in rural communities. Those observations suggest that social stressors in urban settings may affect the development of schizophrenia in persons at risk.

Cultural and Socioeconomic Consideration : Schizophrenia has been described in all cultures and socioeconomic status groups studied. In industrialized nations a disproportionate number of schizophrenic patients are in the low socioeconomic groups. That observation has been explained by the *downward drift hypothesis*, which suggests that affected persons either move into a lower socioeconomic group or fail to rise out of a low socioeconomic group because of the illness. An alternative explanation is the *social causation hypothesis*, which proposes that stresses experienced by members of low socioeconomic groups contribute to the development of schizophrenia.

In addition to hypothesizing that the stress of industrialization causes schizophrenia, some investigators has presented data indicating that the stress of immigration can lead to a schizophrenialike condition. Some studies report a high prevalence of schizophrenia among recent immigrants, and that finding has implicated abrupt cultural change as a stressor involved in the cause of schizophrenia. Perhaps consistent with both hypotheses is the observation that the prevalence of schizophrenia appears to rise among third-world populations as contact with technologically advanced cultures increases.

Advocates of a social cause for schizophrenia argue that cultures may be more or less schizophrenogenic, depending on how mental illness is perceived in the culture, the nature of the patient role, the available system of social and family supports, and the complexity of social communication. Schizophrenia has been reported to be prognostically more benign in less developed nations where patients are reintegrated into their communities and families more completely than they are in highly civilized Western societies.

Homelessness : The problem of the homeless in large cities may be related to the deinstutionalization of schizophrenic patients who were not adequately followed up. Although the exact percentage of homeless persons who are schizophrenic is difficult to obtain an estimated one third to two thirds of the homeless are probably afflicted with schizophrenia.

Financial cost to society : The estimation of an illness's cost to society is a complex task; nevertheless, the financial acknowledged to be enormous. About 1 percent of the United States national income goes toward the treatment of mental illness (excluding substance-related disorders); that percentage came to about $40 billion in 1985. When the indirect costs to society (for example, lost production and mortality) are added, the figure tops $100 billion annually. The majority of that amount is related to covering the direct and indirect costs of schizophrenia.

Mental Hospital Beds : Both the development of effective antipsychotic drugs and changes in political and popular attitudes toward the treatment and the rights of mentally ill people have resulted in a dramatic change in the patterns of hospitalization for schizophrenic patients over the past four decades. The probability of readmission within two years after discharge from the first hospitalization is about 40 to 60 percent. Schizophrenic patients occupy about 50 percent of all mental hospital beds and account for about 16 percent of all psychiatric patients who receive any type of treatment.[28]

Etiology

Environmental Factors

The subsequent development of psychoanalytic theory led to interest in the childhood experiences that might be responsible for the development of schizophrenia. The focus was on the child's interpersonal experience within the family, which might lead to faulty ego development and intrapsychic conflict, which in turn put the child at risk for psychotic regression in adult life. The role of the mother was the first to be cited in the search for a cause. Freida Fromm-Reichmann gave the term *schizophrenogenic mother* to describe the emotionally withholding, domineering, and rejecting attitudes she believed to be present in an excessive number of mothers whose children developed schizophrenia. This, she theorized, led to the child growing up feeling in conflict to, distrustful of, and angry toward others, which later is expressed as a psychotic illness. Other theorists noted evidence of overprotection or rejection in the mothers of schizophrenic individuals.

In the 1950s, interest shifted toward patterns of family or parental interaction that could be responsible for schizophrenia developing in a child. Three major groups of theorists emerged with different hypotheses. Bateson, Jackson, Haley et al.[29] described the concept of the *double-bind* type of communication, which, they argued, could cause schizophrenia in a child who was repeatedly exposed to it. In a double-bind message, meaning is conveyed by communication on different levels or in different modes. For example, literal or metaphorical meaning, verbal expression, and body language. Conflicting messages may thus be given simultaneously, and Bateson suggested that this type of communication could lead to deficits in interpreting meaning, which progress to a disorder of cognition and metacommunication that is seen in schizophrenia.

The possibility remains that types of psychological stresses at critical developmental stages could lead to an increased likelihood of a genetically vulnerable individual developing schizophrenia.

Expressed Emotion : Once established, schizophrenia and the major psychoses have considerable variability in their course and outcome. Only part of this variance is related to response to medication. Thus, environmental influences on the course of illness have become a fertile area of investigation. The course of the illness may be measured by the frequency and severity of relapse and the level of functioning between acute episodes. Follow-up studies of schizophrenic patients returning home have identified certain styles of communication in families that are positively correlated with earlier relapse.[30] The critical factors as measured during a standardized family interview are criticism, hostility, and overinvolvement, know as "expressed emotion" (EE). Based on specific criteria, when families were divided into "high and low" degree of EE there were large differences in relapse rates. These relapse rates were not correlated with severity of illness in the patient. Similar findings were made for families of depressed patients. In high EE families, fewer hours of face-to-face contact between patients and adult relatives significantly reduced the relapse rate in the schizophrenic but not the depressed group of patients. Use of prophylactic medications reduced the relapse rate in schizophrenics returning to high EE homes.

Life Events : Stressful life events seem to relate to the onset of relapse in major psychotic illnesses. Stressors can be divided into those that are acute and independent of the person's behavior and influence (such as an acute illness or death of a relative) and those that are chronic (such as poverty or difficulties at work or in the family environment), which also may be dependent on illness factors in the patient. In the three weeks before a psychotic relapse (in both schizophrenia and depression), it has been shown that there is a high frequency of independent social stressors.[31] Moreover, the use of prophylactic medication in schizophrenics seems to protect against relapse under circumstances of acute stress, unless this is superimposed on a situation of chronic life stress.

Social Class : The role of chronic life stress may be relevant to the finding that schizophrenia clusters in the lower socioeconomic classes (especially in urban environments), something that is not found in other psychotic conditions such as bipolar disorder. A second factor contributing to this clustering is the phenomenon of *social drift*.

The higher representation of schizophrenia in lower socioeconomic classes has been shown to relate in part to the downward mobility experienced by schizophrenic individuals secondary to their disability. Studies of the occupations of both biological and adopted fathers of schizophrenics show that patients frequently fail to reach the occupational level of their parents thus confirming that social drift occurs.

Social Network : The interaction between the effects of the environment on schizophrenia and the effects of schizophrenia on social experience is illustrated again in studies of social network. Social network refers to the circle of family members, friends, and associates with whom support and social activity is shared. Schizophrenics tend to have networks that are smaller, more family oriented, and less intimate than those of controls. Because an individual's social network serves as a major buffer against the stresses of life, the patient's shrinking social network also tends to influence the progression of the illness.

Genetic Factors

There is considerable evidence that schizophrenia is an illness that runs in some families, although the majority of patients evaluated do not have a first-degree relative (for example, sibling, parent, or child, each of whom probably shares half of the patient's genes) with schizophrenia. The morbid risk of a schizophrenic patient's first-degree relative developing schizophrenia is approximately between 4 and 9 percent, based on different studies. Family members more distantly related to a schizophrenic patient have a lesser risk for the development of schizophrenia. What exactly is transmitted is not clear. Twin studies report that monozygotic twins are more likely to be concordant for schizophrenia (range in different studies 31-78 percent) than dizygotic twins (range in different studies 0-28 percent). However, the concordance for monozygotic twins is not absolute, suggesting that the illness is transmitted only in a subset of the twins or that environmental influences can have either a triggering or protective influence in individuals. Twinning might cause vulnerability to the development of a number of conditions, including schizophrenia.

Various studies have shown that the likelihood of monozygotic twin being concordant for schizophrenia is over *four times* greater than that for dizygotic twins. It is important to note that approximately 50 percent of monozygotic twin pairs are discordant for schizophrenia, suggesting that what is transmitted is not the illness per se but the vulnerability for the development of it. Adoption studies of offspring of schizophrenic patients show that they have a greater likelihood of developing schizophrenia than do the adopted offspring of healthy individuals. The estimated heritability of a diathesis for schizophrenia based on such studies is between 60 and 90 percent.

Advances in molecular biology allow chromosomal analysis in which a search for linkage with known genetic markers can be done in families in which schizophrenia is prevalent. The gene that transmits schizophrenia is reported to sit in close proximity to a known DNA marker on the fifth chromosome in one study of a large extended family, though a number of attempts to replicate this finding have failed. Questions about the statistical assumptions used in studies like this have been raised. Failure to replicate the original report could also be the result of the heterogeneity of schizophrenia. Another approach is to explore candidate genes, i.e., D2 receptor gene, as possibly involved in the transmission of schizophrenia. Attempts to link candidate genes to schizophrenia have failed so far.

Schizophrenic mothers are more likely to have pregnancy problems and perinatal problems with their children; thus, patients might have not only the genetic diathesis but also environmental insults both intrauterine and perinatally. Furthermore, children of schizophrenic mothers are more likely to have disruptive early life experiences that make developmental aberrations, including psychological ones, more likely.

There is a complex interaction between the genetic influences and environmental variables leading to the phenotypic expression of schizophrenia. These variables are interactive, not only the development of schizophrenia but also its course. In different individuals, differing genetic and environmental factors may thus play lesser or greater roles in cause and pathogenesis, thus contributing, particularly in schizophrenia, to the

heterogeneity of the disorder. The most widely accepted view of the pathogenesis of schizophrenia is the *stress diathesis* model, in which constitutional factors determined by heredity (the diathesis) interact with environmental influences (stress) that precipitate overt expression of the clinical symptoms.

Anatomical Factors

Neuropathological studies of postmortem schizophrenic brains have attempted to find lesions that would explain the symptoms of schizophrenia. The search for pathological lesions in schizophrenia has focused on the frontal and medial temporal lobes, particularly the hippocampus suggesting a developmental rather than a degenerative disturbance. However, there is still insufficient evidence to clearly indicate a specific site for a pathological lesion in all schizophrenic patients.

Although a resurgence of interest exists in postmortem neuropathological studies of schizophrenic brains, there are a number of potential pitfalls in this methodology. These include the difficulty in dissociating the etiological factors from effects that might be the result of long-term chronic illness and effects of treatment. Other difficulties include changing ideas about diagnosis, the question of appropriate controls, the cause of death, delays in obtaining and fixing the brain after death, and so forth. Neurochemistry also has been used in postmortem studies to unravel the mysteries of schizophrenia. A number of studies have documented increases in the number of type 2 dopamine (D_2) receptors in areas such as the basal ganglia and nucleus accumbens, although such an increase could be the result of neuroleptic treatment.

Imaging techniques, as they have become available, have been used to better understand the morphology and pathophysiology of schizophrenia. Computed tomography (CT) allows a noninvasive technique to be used to obtain X-rays of the brain in transverse slices. Numerous studies have documented enlargement of the lateral ventricles, increased width of the third ventricle, and sulcal enlargement suggestive of cortical atrophy. Lateral ventricular enlargement is reported in schizophrenic patients in

the vast majority of controlled studies. Enlargement of the lateral ventricles is not necessarily sufficient to be read as clinically abnormal in the majority of schizophrenic patients. However, planimetric and automated measurements clearly show that statistically significant enlargement of the lateral ventricle exists in the majority of schizophrenic patients. Not all schizophrenic patients have enlarged lateral ventricles, so that enlargement of the lateral ventricles is neither sufficient nor necessary for the diagnosis of schizophrenia. Lateral ventricular enlargement is not specific to schizophrenia. It found in a number of neurological conditions and also in non-schizophrenic psychiatric conditions such as bipolar disorder.

In monozygotic twins discordant for schizophrenia, the lateral ventricles of the schizophrenic twin are enlarged compared with those of the healthy twin. The lateral ventricular enlargement is seen very early in the onset of the illness, suggesting that it proceeds the psychosis. Preliminary data suggest that the finding is not progressive. Lateral ventricular enlargement has been correlated with cognitive disturbances, negative symptoms, poor premorbid psychosocial functioning, poor response to treatment, and poor outcome.

The third ventricle is situated close to anatomical areas of particular interest in schizophrenia. It has been measured in a number of studies, and the majority report its enlargement. Sulcal enlargement also had been reported in a significant number of schizophrenic patients, suggesting diffuse cortical atrophy.

Magnetic resonance imaging (MRI) techniques provide significant advantages over CT scan studies, including better resolution; lack of exposure to radiation; the capacity to have transverse, sagittal, and coronal cuts; and the capacity to do three-dimensional reconstruction of the brain. MRI studies generally confirm the CT findings of enlarged lateral ventricles. In addition, some studies report a 3-5 percent reduction in total brain area and/or volume in schizophrenia. An MRI study also supported the CT study of the affected co-twin with schizophrenia having larger lateral ventricles. MRI studies

focusing on the temporal lobe and limbic structures report a reduction in temporal lobe, hippocampal, and amygdala volumes in schizophrenia. The abnormalities are found more often on the left side.

Physiological Factors

Physiological studies connect mental function to underlying physiological processes that are measurable and thus provide insights into normal and pathological psychic functioning. Physiological studies of cerebral blood flow in schizophrenia have been done with xenon 133 inhalation, positron emission tomography (PET), and single photon emission computed tomography (SPECT). There does not seem to be a difference in the total cerebral blood flow between schizophrenic patients and normal controls. Attempts to study differences in the resting state have resulted in inconsistent results. A number of studies have suggested a "*hypofrontal pattern*" to the regional distribution of cerebral blood flow with a relative decrease of blood flow to the frontal lobes.

Biochemical Factors

The search for a biochemical understanding of schizophrenia have been plagued by numerous discoveries that have failed to be replicated. The dopamine system has been a primary focus as a mediator of pathology that could explain the illness of schizophrenia. There is mostly indirect evidence to support a causal role of dopamine in schizophrenia. Thus, all typical neuroleptics have the common capacity to block D_2 (non -adenylate cyclase) dopamine receptors. Furthermore, indirect dopamine agonists have the capacity to induce a condition that is clinically indistinguishable from schizophrenia or exacerbate a psychotic condition, although neither of these effects is consistent in all patients. The affinity that various neuroleptic agents had for the D_2 receptor correlated highly with the average therapeutic dose used for the control of psychotic symptoms. Such data strongly suggest that the neuroleptic action at the D2 receptor is pharmacologically relevant for the clinical benefits.

Because both the limbic and prefrontal cortex have dopamine projections from the midbrain, it is interesting to look at these systems and their relation to pathology in schizophrenia. There are some differences between the mesocortical and mesolimbic dopamine pathways. The mesocortical dopamine pathway, like the tuberoinfundibular one, does not seem to have autoreceptors on the cell bodies and nerve terminals (Bannon and Roth, 1983). It is believed that as a result of this lack of autoreceptors, the mesocortical dopamine neurons have a higher rate of physiological activity, are less responsive to dopamine agonists and antagonists, and do not develop tolerance to chronic neuroleptic treatment. Thus, it is possible that neuroleptics are used at therapeutic doses that have their predominant effect on the nigrostriatal and the mesolimbic dopamine systems, which result I control of the positive psychotic symptoms and the development of extrapyramidal side effects. At higher doses, neuroleptics may also have an effect on the mesocortical system thereby they can exacerbate negative symptoms.

There is a growing body of evidence suggesting that cell migration, sympase formations, and programmed cell death might be abnormal in the frontal and temporal cortex and the hippocampus and surrounding areas in schizophrenia. Cell migration is most intense in the early and middle second trimester. Such a period of development might be particularly vulnerable to specific viral infections, failure of gene expression, or other etiological mechanisms that can leave the individual vulnerable to the development of schizophrenic symptoms during adulthood. The influenza epidemic in 1957 has been associated with an increased incidence of schizophrenia in children whose mothers were in the second trimester of pregnancy.

Acute treatment with neuroleptic agents results in an increase in the firing rate of the dopamine cells and an increasing turnover of dopamine at the synaptic sites. However, chronic treatment results in a decrease in the firing rate related to depolarization block of the dopamine cells and the down-regulation of the receptor sensitivity. This is reflected in the reduction of both plasma and cerebrospinal fluid (CSF) homovanillic acid

(HVA), a metabolite of dopamine. This reduction in HVA is temporally associated with clinical improvement.

Thus, a number of different lines of information from the clinical, anatomical, physiological, biochemical, and pharmacological areas are coming together to aid in understanding the complex enigma of schizophrenia, no single etiologic factor is considered causative.[32]

Clinical Features

The clinical signs and symptoms of schizophrenia raise three key issues. First, no clinical sign or symptom is pathoginomonic for schizophrenia; every sign or symptom seen in schizophrenia can be seen in other psychiatric and neurological disorders. That observation is contrary to the often-heard clinical opinion that certain signs and symptoms are diagnostic of schizophrenia. Therefore, a clinician cannot diagnose schizophrenia simply be a mental status examination. The patient's history is essential for the diagnosis of schizophrenia. Second, a patient's symptoms change with time. For example, a patient may have intermittent hallucinations and a varying ability to perform adequately in social situations. Or, for another example, significant symptoms of a mood disorder may also come and go during the course of schizophrenia. Third, the clinician must take into account the patient's educational level, intellectual ability, and cultural and subcultural membership. An impaired ability to understand abstract concepts, for example, may reflect the patient's education or intelligence. Various religious organizations and cults may have customs that seem strange to those outside that organization but that are considered perfectly normal to those within the cultural setting.

Premorbid Signs and Symptoms

In theoretical formulations of the course of schizophrenia, premorbid signs and symptoms appear before the prodromal phase of the illness. That differentiation implies

that premorbid signs and symptoms exist before the disease process evidences itself and that the prodromal signs and symptoms are parts of the evolving disorder. The typical but not invariable premorbid history of schizophrenic patients is that they had schizoid or schizotypal personalities. Such a personality may be characterized was quiet, passive, and introverted; as a result, the child had few friends. A preschizophrenic adolescent may have had no close friends and no dates and may have avoided team sports. Such an adolescent may enjoy watching movies and television or listening to music to the exclusion of social activities.

The prodromal signs and symptoms are almost invariably recognized retrospectively after the diagnosis of schizophrenia has been made. Therefore, their validity is uncertain; once schizophrenia is diagnosed, the retrospective remembrance of early signs and symptoms is affected. Nevertheless, although the first hospitalization is often considered the beginning of the disorder, signs and symptoms have often been present for months or even years. They may have started with complaints about somatic symptoms, such as headache, back and muscle pain, weakness, and digestive problems. The initial diagnosis may be malingering or somatization disorder. Family and friends may eventually notice that the person has changed and is no linger functioning well in occupational, social, and personal activities. During that stage the patient may begin to develop a new interest in abstract ideas, philosophy, the occult, or religious matters. Additional prodromal signs and symptoms may include markedly peculiar behavior, abnormal affects, unusual speech, bizarre ideas, and strange perceptual experiences.[33]

Symptoms of Schizophrenia

Psychotic symptoms are marked by abnormalities in the form of thought, content of thought, perceptual disturbances, and alterations in emotions and behavior.[34]

Formal thought disorder is an abnormality in the form of thought. It is differentiated from lack of speech, which is called poverty of speech. The extreme form of poverty of

speech can present itself as muteness. Examples of formal thought disorders are as follows :

a). *Derailment* or *loose associations* is a condition in which the sequential connection between ideas is difficult or impossible to follow because the patient wanders to relatively or totally unrelated subjects. This can be present in a single sentence or in a series of sentences.

b). *Tangentiality* is the tendency to wander to points that are distantly connected, but be unable to return spontaneously to the original point. Returning to the original line of thought through a circuitous route is called *circumstantiality*.

c). *Incoherence* is a condition in which even sentences are impossible to follow. It is different from derailment and loose associations, in which the connections between clauses or sentences are problematic. Lack of understanding because of incomprehensible verbalization of speech is excluded from this description.

Delusions are the result of an abnormality in the content of thought. Delusions are false beliefs that are often fixed and cannot be explained based on the cultural background of the individual. If the intensity of the delusions is minor, patients may have some insight into their nonsensical nature and therefore may doubt them. The intensity of a delusion is based on how firmly the belief is held, lack of insight, whether the delusion preoccupies the individual to the exclusion of other concerns, and whether the individual bases his actions on the delusion. The different types of delusions are as follows :

a). *Paranoid* delusions are convincing feelings that one is being persecuted, in the absence of such a reality. Paranoid patients may believe that they are being followed, their personal belongings are being tampered with, their telephone is tapped, and they are being harassed.

b). *Ideas and delusions of reference* occur when the patient believes that some event, often of no consequence, is related to them specifically. Often the delusions can have a paranoid flavor, whereby someone talking in the distance is misinterpreted as talking about and having designs on the patient; or a statement made on the radio or television has special reference to the patient. The questioning of these beliefs by the

patient would make them ideas of reference, while their acceptance as reality would make them delusions.

c). *Delusion of being controlled* is the belief that one's actions are under the control of someone or some external force with malicious intent. The patient feels powerless in the face of such a force and will often relinquish responsibility for their actions or thoughts. The voluntary release of control over one's beliefs and actions, which is seen in cult situations, is not delusional because control is real and given voluntarily.

d). *Thought broadcasting* is the delusion that one's thoughts are broadcast so that they can be heard by others or transmitted to others even in the absence of vocalizations. Some patients might feel that their thoughts are heard audibly by themselves, or that their mind their mind can be read by someone, even in the absence of verbalization.

e). *Thought insertion and withdrawal* are delusions that the patient's mind is having alien thoughts inserted or thoughts withdrawn outside of their control.

f). *Delusions of jealousy* are ones in which the individual believes that a loved one is being unfaithful, in the absence of such a reality. The love might be real or imagined.

g). *Delusions of guilt* are ones in which patients feel that, by acts of omission or commission, they are guilty of some deed for which they blame themselves excessively. Often the delusion is based on an insignificant detail in the patient's past that he or she is unable to forget. At times the patient will confess to being to cause of major catastrophes and will focus attention on confessing a deed that is obviously not of their doing. Delusions of guilt are often in the context of overzealous religious beliefs. Delusions of guilt are not specific for schizophrenia and are also common in psychotic depressions.

h). *Grandiose delusions* are delusions in which the patient believes they have special powers that are beyond those of the normal individual. The patient may think that he or she is someone special, such as Jesus or the president, or believe that they have a special mission or significance to society and the world. A paranoid flavor is at times associated with grandiose delusions. Grandiose delusions are often associated with manic states and frequently are accompanied by excess irritability. Because paranoid

delusions can be present in mania, they provide little help in differentiating schizophrenia from manic psychosis.

l). *Religious delusions* also are a frequent phenomenon and include exaggerations of conventional religious beliefs. The beliefs have to be taken within a sociocultural context before they are labeled as delusional. These can be seen in schizophrenic and affective psychoses.

j). *Somatic delusions* are false beliefs related to the body. These frequently take the form that the body or a part of it is rotting or does not exist. Similar delusions may occur in major depression with psychotic features.

Hallucinations are the experiencing of stimuli in any of the senses in the absence of external stimulation. Based on the particular sense involved, the hallucination is called auditory, visual, tactile, olfactory, or gustatory. In functional psychotic conditions, auditory hallucinations are frequent, visual hallucinations are relatively uncommon, and hallucinations in the other senses are rare. The presence of visual hallucinations should raise the possibility of primary neurologic disorders or the presence of metabolic or toxin, drug, medication-induced delirium, whereas the presence of olfactory hallucinations should raise the likelihood of seizure disorders, especially complex partial seizures.

Auditory hallucinations are the most frequently reported hallucination in schizophrenic patients. These include one or more voices talking to or about the patient. Infrequently calling the patient by name is not by itself evidence that the patient is schizophrenic, but continuous hallucinations lasting all day or on and off for a couple of weeks ore indicative of a schizophrenic psychosis. Typically, the patient experiences them as unpleasant, although he or she can get used to they and miss them in their absence. The voices can keep a running commentary of the patient's actions as they happen or can predict actions. The auditory hallucinations can be heard either inside the patient's head or coming from outside. At times, patients responding to treatment will report the progression of voices from outside to inside the head, to audible thoughts that may initially be alien but may later be their own before they go away. Auditory hallucinations of a

self-critical or damning nature also may appear in major depression with psychotic features.

Visual hallucinations that occur with the use of hallucinogenic drugs or transiently just as the patient is about to fall asleep (hypnagogic) or wake up (hypnopompic) should not be considered schizophrenic in nature.

Bizarre behaviors include socially inappropriate behaviors such as dressing totally out of context or disinhibition of behavior that would not be socially accepted, such as masturbating in public. The sociocultural contexts of the behavior should be taken into consideration before they are labeled as bizarre. Stereotyped behaviors are repetitive part actions, often symbolic, that have some contextual meaning to the patient.

Catatonic behavior is the presence of a marked reduction of psychomotor activity. This may present as rigidity, causing passive resistance to movement, or waxy flexibility, in which the patient maintains postures induced by the examiner. Lesser forms of catatonic behavior include mutism and negativism (passive resistance to any attempt to move).

Affect is the outward expression of emotion and is observed in facial features that routinely accompany the experience of emotions during communication. In schizophrenic patients there is a paucity of emotional expression or affect, and terms such as emotional blunting or flat affect are used to describe this situation. A dissociation between affect and behavior or cognition is described as incongruent affect.[35]

Types of Schizophrenia

1. Catatonic
    a. Stupor or mutism
    b. Negativism
    c. Rigidity

d. Purposeless excitement

e. Posturing

2. Disorganized

a. Incoherence, marked loosening of associations, or grossly disorganized behavior

b. Flat or grossly inappropriate affect

c. Does not meet criteria for catatonic type

3. Paranoid

a. Preoccupation with systematized delusions or with frequent auditory hallucinations related to a single theme.

b. None of the following : incoherence, loosening of associations, flat or grossly inappropriate affect, catatonic behavior, grossly disorganized behavior.

4. Undifferentiated type

a. Prominent delusions, hallucinations, incoherence, or grossly disorganized behavior

b. Does not meet the criteria for paranoid, catatonic, or disorganized type

5. Residual type

a. Absence of prominent delusions, hallucinations, incoherence, or grossly disorganized behavior

b. Continuing evidence of the disturbance through two or more of the residual symptoms

6. Type I and Type II

A more recently suggested system proposes classification of schizophrenic patients into type I and type II. This system is based on the presence of positive or negative symptoms, sometimes referred to, respectively, as productive and deficit symptoms. The deficit symptoms include affective flattening or blunting, poverty of speech or speech content, blocking poor grooming, lack of motivation, anhedonia, social withdrawal, cognitive defects, and attentional deficits. Positive symptoms include loose

associations, hallucinations, bizarre behavior, and increased speech. Type I patients have mostly positive symptoms, and type II patients have mostly negative symptoms.

Differential Diagnosis

Organic Mental Disorders. Present with impaired memory, orientation and cognition; visual hallucinations; signs of CNS damage. Many neurologic and medical disorders can present with symptoms identical to those of schizophrenia, including substance-induced organic mental disorders, vascular disorders, complex partial seizures, and degenerative disease.

Schizophreniform Disorder. Symptoms may be identical to schizophrenia, but are of less than 6 months duration. There is also less deterioration and a better prognosis.

Brief Reactive Psychosis. Symptoms are of less than 1 month duration and are secondary to a clearly identifiable psychosocial stress.

Mood Disorders. Both bipolar disorder and major depression may present with psychotic symptoms similar to schizophrenia. The differential is particularly important because of the availability of specific and effective treatments for the mood disorders. Also, if hallucinations and delusions are present in a mood disorder, they develop after the mood disturbance and do not persist. Other factors that help differentiate moo d disorders from schizophrenia include family history, premorbid history, course, prognosis, and response to treatment.

Schizoaffective Disorder. Mood symptoms develop concurrently with symptoms of schizophrenia, but delusions or hallucinations must be present for 2 weeks in the absence of prominent mood symptoms during some phase of the illness. The prognosis of this disorder is better than that expected for schizophrenia and worse than that for mood disorders.

Atypical Psychosis. A psychosis in which there is a confusing clinical feature, such as persistent auditory hallucinations as the only symptom, or specific culture-bound psychoses.

Delusional Disorders. Nonbizarre, systematized delusions of at least 6 months duration in the context of an intact, relatively high-functioning personality and in the absence of prominent hallucinations or other schizophrenic symptoms. Onset is in middle to late adult life

Personality Disorders. Generally without psychotic symptoms and, if present, tend to be transient and not prominent. Most important personality disorders in this differential are schizotypal, schizoid, borderline, and paranoid.

Factitious Disorder with psychological symptoms and malingering. No lab test or biologic marker can objectively confirm the diagnosis of schizophrenia. Schizophrenic symptoms are therefore possible to feign for either clear secondary gain (malingering) or deeper psychologic motivations (factitious disorder).

Pervasive Developmental Disorder (infantile autism). This diagnosis is made if onset is between 30 months and 12 years. Although behavior may be quite bizarre and deteriorated, there are no delusions, hallucinations, or clear formal thought disorder, e.g., loosening of associations.

Mental Retardation. May have similar intellectual, behavioral, and mood disturbances, which suggest schizophrenia. Generally, however, there are no overt psychotic symptoms, and there is a constant low level of functioning rather than a deterioration. If psychotic symptoms are present, a diagnosis of schizophrenia may be made concurrently.

Shared Cultural Beliefs. Odd beliefs shared and accepted by a cultural group and thus not considered psychotic.

Course and Prognosis

Course : Prodromal symptoms of anxiety, perplexity, terror, or depression generally precede the onset of schizophrenia, which may be acute or insidious. Prodromal symptoms may be present for months before definitive diagnosis is made. Onset is generally in the late teens and early 20s. Precipitating events, such as emotional trauma, drugs, and separations, may trigger episodes of illness in those predisposed. Classically, the course of schizophrenia is one of deterioration over time, with acute exacerbations superimposed on a chronic picture. Vulnerability of stress is lifelong. Postpsychotic depressive episodes may occur In the residual phase. Over the course of the illness, the more florid positive psychotic symptoms, such as bizarre delusions and hallucinations, tend to diminish in intensity, while the more residual negative symptoms, such as poor hygiene, flattened emotional response, and various oddities of behavior, may actually increase. Relapse rates are approximately 40 percent in 2 years on medication and 80 percent in 2 years off medication. Suicide is attempted in 50 percent of patients; 10 percent are successful. Violence is not greater than in general population. There is increased risk of sudden death, medical illness, and shortened life expectancy.

Prognosis : Schizophrenic patients in nonindustrialized, developing countries have better prognosis than do patients in industrialized, western societies.

Table 1: Prognosis of Schizophrenia[36]

GOOD PROGNOSIS	POOR PROGNOSIS
1. Acute onset with obvious precipitating factor	1. Insidious onset with no precipitating factors
2. Good premorbid social and work history	2. Poor premorbid social and work history
3. Mood symptoms (especially depression)	3. Withdrawn, autistic behavior
4. Paranoid subtype	4. Disorganized and undifferentiated subtypes.
5. Possibly catatonic subtype	5. Not married
6. Married	6. Family history of schizophrenia
7. Family history of mood disorder	7. History of difficult delivery
8. Predominance of positive symptoms	8. Presence of neurologic signs and symptoms
9. Confusion	9. Predominance of negative symptoms
10. Tension, anxiety, hostility	10. Absence of mood symptoms or overt hostility

In terms of overall prognosis, some investigators have described a loose rule of thirds: approximately 1/3 of patients lead somewhat normal lives, 1/3 continue to experience significant symptoms but are able to function within society, and the remaining 1/3 may be markedly impaired and require frequent hospitalizations. Approximately 10 percent of this final third of patients require chronic institutionalization.[36]

Treatment

Psychopharmacologic

choice of drug : 1. chlorpromazine [Thorazine] - low potency ; used in hyperactive or agitated patient.

2. trifluoperazine [Stelazine] - high potency ; used in withdrawn or lethargic.

3. Clozapine [Clozaril] - atypical neuroleptic ; used in resistant cases

maintenance : after signs and symptoms abate and patient is stablized (usually after 4 weeks), dosage can be reduced to lowest level to maintain withdrawn for trial period to see if relapse occurs, at which point therapy is reinstituted. Some patients may be on lifelong maintenance therapy to prevent relapse.

Adverse side effects : If traditional neuroleptic alone is ineffective, several other drugs have been reported to cause varying degrees of improvement. The addition of propranolol (Inderal), benzodiazepines, and carbamazepine (Tegretol) have been reported to lead to improvement in some cases.

Table 2 : Neuroleptic Treatment[36]

Drug	Average daily oral dose range, mg	Potency ratio compared with 100 mg chlorpromazine
Phenothiazines :		
Aliphatics :		
Chlorpromazine (Thorazine)	400 - 800	1: 1
Piperazines :		
Fluphenazine (Prolixin)	4-20	1: 50
Fluphenazine enanthate or decanoate	25-100*	
Perphenazine (Trilafon)	8-32	1: 10
Trifluoperazine (Stelazine)	6-20	1: 20
Piperidines :		
Thioridazine (Mellaril)	200-600	1: 1
Butyrophenones :		
Haloperidol (Haldol)	8-32	1: 50
Haloperidol decanoate	+	1: 50
Thioxanthenes :		
Chlorprothixene (Taractan)	400-800	1: 1
Thiothixene (Navane)	15-30	1: 25
Oxoindoles :		
Molindone (Moban, Lidone)	40-200	1: 10
Dibenzoxazepines :		
Loxapine (Loxitane)	60-100	1: 10

*Intramuscular injection, long-acting, every 1-3 weeks

+Intramuscular injection, long-acting, administered at monthly intervals. Initial dose should not exceed 100 mg, and clinical experience at doses greater than 300 mg/month has been limited.

Electroconvulsive Therapy

Used effectively in small percentage of schizophrenic patients, particularly those of the catatonic subtype. Patients with an illness duration of less than 1 year are most responsive.

Psychosocial

Neuroleptics medication alone is not as effective in treating schizophrenic patients as when the drugs are coupled with psychosocial interventions.

Behavior therapy : desired behaviors are positively reinforced by rewarding targeted behaviors with specific tokens, such as trips or privileges. Intent is for reinforced behavior to generalize to the world outside of hospital ward.

Group therapy : focus is on support and social skills development (activities of daily living). Groups are especially helpful in decreasing social isolation and increasing reality testing.

Family therapy : family therapy techniques can significantly decrease relapse rates for the schizophrenic family member. High expressed emotion family interaction can be diminished through family therapy. Multiple family groups, in which family members of schizophrenic patients discuss and share issues, have been particularly helpful in this regard.

Supportive psychotherapy : traditional insight-oriented psychotherapy is not recommended in treating schizophrenic patients, whose egos are too fragile. Supportive therapy, which is generally the therapy of choice. The rule is that as much insight as a patient desires and can tolerate is an acceptable goal.[36]

Atypical Neuroleptics

History

During the last half century, typical neuroleptics have been extensively studied. It has been incontrovertibly demonstrated that they can alleviate the positive symptoms of schizophrenia and prevent their recurrence. Thus, typical neuroleptics have been shown to be effective agents in the acute and maintenance treatment of schizophrenia. At the same time, however, the limitations of this class of compounds have become painfully apparent. First, typical neuroleptics produce very high side effect rates, particularly by their actions on the extrapyramidal system, which can lead to signs of parkinsonism, dystonia, kathisia, and tardive dyskinesia.[37] Second, not all patients will experience therapeutic responses to these compounds. Moreover, only one dimension of the morbidity of schizophrenia (positive symptoms) can be expected to respond to treatment. Typical neuroleptics are less effective or wholly ineffective against the negative symptoms and the neurocognitive deficits of the illness.[38]

Clozapine has provided the first genuine advance in neuroleptic efficacy since chlorpromazine. Just as chlorpromanzine was the prototype for typical neuroleptic that followed it from 1954 to 1985, clozapine has become a prototype for the next generation of compounds called *atypical neuroleptics*. The increased selectivity of the new generation neuroleptics is the result of rational drug development. Pharmaceutical companies, in order to produce the next generation of neuroleptics, have designed drugs with selective properties. Atypical neuroleptics are defined by various preclinical and clinical properties (Table 3).

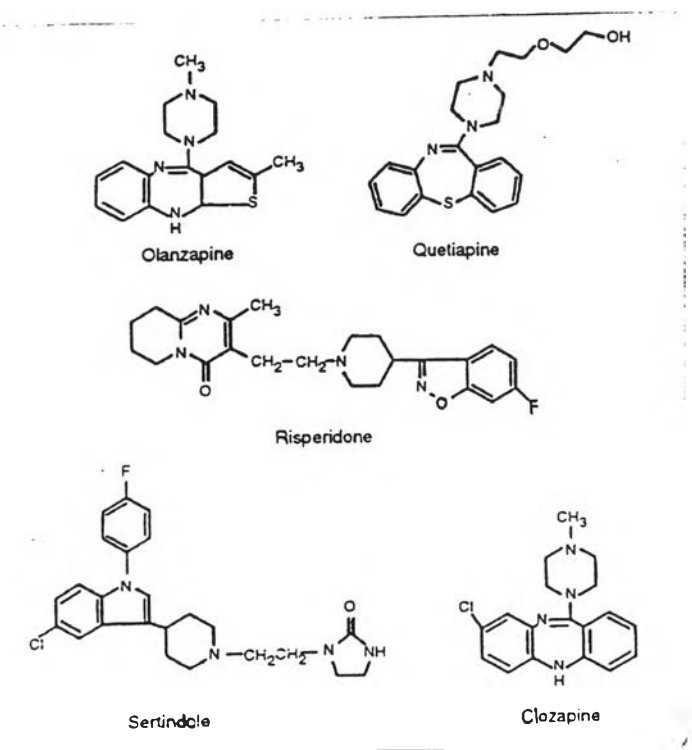
Table 3 : Properties of Atypical Neuroleptics[13]

- Alleviate psychotic symptoms
- Alleviate negative symptoms
- Alleviate neurocognitive deficits
- Effective in refractory patients
- Cause less or no extrapyramidal side effects
- Cause less or no tardive dyskinesia
- No sustained elevation of prolactin

Classification of Atypical Neuroleptics

Since the opening of clozapine in February 1990 had led to establishment of a new group neuroleptics. In February of 1994, risperidone was released. After a while, other four additional atypical neuroleptics followed. These include olanzapine, seroquel, and sertindole.

Figure1: Structures of Atypical Neuroleptics[39]



Clozapine (Clozaril) is a member of the dibenzodiazepine class of neuroleptics. The drug has a pharmacologic profile unlike typical neuroleptics and is labeled as an atypical neuroleptics. Its most severe side effect is agranulocytosis. A weekly blood monitor must be done to prevent this side effect on clozapine's user.

Risperidone (Risperdal) is a benzsoxazole derivative. It is a medication for treating schizophrenia and psychotic disorder. It helps manage schizophrenia's positive and negative symptoms. Unlike clozapine, risperidone's side effects are usually minor and blood monitoring is not necessary.

Olanzapine (Zyprexa), a thienobenzodiazepine, is an atypical neuroleptics. It is indicated for the acute and maintenance treatment of schizophrenia and related psychotic disorders. It also found to improve both positive and negative symptoms.

Seroquel (Quetiapine) has a broad receptor binding profile, with greater affinity for 5-HT2 receptors that for D_2 receptors. Such a profile is widely accepted to be indicative of atypicality. Seroquel has demonstrated consistent efficacy in the treatment of schizophrenia.

Sertindole (Serlect) is an atypical neuroleptics similar to clozapine or risperidone. Sertindole works as well as typical neuroleptic, but with fewer movement disorders. It is saved for second line therapy because there is the concern that it may cause arrhythmias. Therefore, people with existing cardiac problems should use it only with medical supervision.

Olanzapine

Olanzapine fits the definition of "atypicality" by having less extrapyramidal side effects liability and greater positive symptom efficacy than the typical neuroleptics. In fact, olanzapine seems to have many of the advantages of clozapine (for example: few extrapyramidal side effects, relatively low elevation of prolactin levels), while at the same time olanzapine is spared some of clozapine's major difficulties (for example: no evidence of agranulocytosis, does not seem more likely to cause seizures than the typical neuroleptics).

Therapeutic Classification :

Olanzapine is an antipsychotic agent. (neuroleptics)

Pharmaceutical Form :

Olanzapine comes as coated tablets for oral administration with 5mg., 7.5mg., and 10mg. of olanzapine activity.

Pharmacology :

Pharmacodynamic Properties - Olanzapine, a thienobenzodiazepine, is an antipsychotic agent, displaying high receptor affinity binding in vitro at serotonin 5-$HT_{2A/C}$, 5 HT_3, 5 HT_6; dopamine D_1, D_2, D_3, D_4, D_5; muscarinic $M_{1\text{-}5}$; adrenergic α_1; and histamine H1 receptors. In a behavioral paradigm predictive of neuroleptics activity, olanzapine reduced conditioned avoidance response in rats at doses lower than 4 times those required to produce catalepsy. In a single dose (10mg.), olanzapine produced higher 5-HT_{2A} than dopamine D_2 receptor occupancy. The percent of D_2 occupancy was less than the threshold value predictive of extrapyramidal events.

Olanzapine also demonstrated greater in vivo serotonin $5HT_2$ activity compared to dopamine D_2 receptor affinity and activity. Electrophysilogical studies demonstrated that

olanzapine selectively reduced the firing of mesolimbic dopaminergic neurons, while having little effect on the striatal pathways involved in motor function

Pharmacokinetic Properties : Olanzapine is well absorbed after oral administration, reaching peak plasma concentrations within 5 to 8 hours. The absorption is not affected by food Plasma concentrations of olanzapine were linear are dose proportional in trials studying doses from 1 to 20 mg.

Olanzapine is metabolized in the liver by conjugative and oxidative pathways. The major circulating metabolite is the 10-N-glucuronide, which in theory does not pass the blood-brain barrier. Cytochrome P450 isoforms CYP1A2 and CYP2D6 contribute to the formation of the N-desmethyl and 2-hydroxymethyl metabolites. Both metabolites exhibited significantly less in vivo pharmacological activity than olanzapine in animal studies. The predominant pharmacologic activity is from the parent olanzapine.

After oral administration to healthy subjects, the mean terminal elimination half-life was 33 hours and the mean olanzapine plasma clearance was 26L/hr. Olanzapine pharmacokinetics varied on the basis of smoking status, gender and age. But the magnitude of the impact of these single factors is small in comparison to the overall variability between individuals.

There was no significant difference in mean elimination half life or olanzapine plasma clearance between subjects with severely impaired renal function compared to individuals with normal renal function. Approximately 57 percent to radiolabeled olanzapine is excreted in urine, principally as metabolites. Subject with mild hepatic dysfunction who smoked had reduced clearance comparable to nonsmoking subjects with no hepatic dysfunction.

In a study of Caucasians, Japanese, and Chinese subjects, there was no differences in olanzapine pharmacokinetics among the three populations. Cytochrome P450 isoform CYP2D6 status does not affect the metabolism of olanzapine.

Dosage and Administration :

Adult : Olanzapine should be administered on a once-a-day schedule without regard to meals, generally beginning with 5 to 10 mg, with a target dose of 10 mg per day within several days. Further dosage adjustments, if indicated, should generally occur at intervals of not less than 1 week, since steady state for olanzapine would not be achieved for approximately 1 week in the typical patient. When dosage adjustments are necessary, dose increments/decrements of 5 mg are recommended. An increase to a dose greater than target dose of 10 mg per day is normally recommended only after clinical assessment. The safety and efficacy of doses above 20 mg per day have not been evaluated.

The elderly or debilitated patient : In clinical trials, 44 patients with schizophrenia or related disorders, 65 years of age or over, were treated with olanzapine (5-20 mg daily). Given the limited experience with olanzapine in the elderly, and the higher incidence of concomitant illness and concomitant medication in this population, olanzapine should be used with caution.

The recommended starting dose in 5 mg in patients who are elderly, debilitated, who hove a predisposition to hypotensive reactions, who otherwise exhibit a combination of factors that may result in slower metabolism of olanzapine, or who may be pharmacodynamically more sensitive to olanzapine. When indicated, dose escalation should be performed with caution in these patients.

Patients with Hepatic and/or Renal Impairment : As clinical experience is lacking in these patients the lower initial starting dose and slower titration to initial target

dose should be considered. Further dose escalation, when indicated, should be conservative.

Maintenance Therapy : It is recommended, that responding patients be continued on olanzapine at the lowest dose needed to maintain remission. Patients should be reassessed periodically to determine the need for maintenance treatment. While there is no body of evidence available to answer the question of how long the patient should be treated with olanzapine, the effectiveness of maintenance treatment is well established for many other neuroleptics.

Therapeutic Indications :

Olanzapine is indicated for the acute and maintenance treatment of schizophrenia and other psychoses where positive symptoms (for example: delusions, hallucinations, disordered thinking, hostility, and suspiciousness) and/or negative symptoms (for example: flattened effect, emotional and social withdrawal, poverty of speech) are prominent. Olanzapine also alleviates the secondary affective symptoms commonly associated with schizophrenia and related disorders. Olanzapine is effective in maintaining the clinical improvement during contunuing therapy in patients who have shown initial treatment response.

Contraindications :

Olanzapine is contraindicated in patients with a known hypersensitivity to the drug or any ingredient of the product.

Warnings :

Neuroleptic Malignant Syndrome (NMS) : In clinical trials, there were no reported cases of NMS in patients receiving olanzapine. However, NMS, a potentially fatal syndrome complex, has been reported in association with other neuroleptics. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia,

diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatinine phosphokinase, myoglobinuria, and acute renal failure. Clinical manifestations of NMS or the presence of high fever without clinical manifestations of NMS require discontinuation of all neuroleptics, including olanzapine.

Tardive Dyskinesia (TD) : Tardive dyskinesia a syndrome consisting of potentially irreversible involuntary dyskinetic movements, is associated with the use of neuroleptics. Tardive dyskinesia occurs more frequently in elderly patients, however, patients of any age can be affected. It is unknown whether neuroleptics may differ in their potential to cause TD. However, during long-term, double-blind extension maintenance trials, olanzpine was associated with a statistically significantly lower incidence of treament emergent dyskinesia compared to haloperidol.

The risk of developing TD and the chance of it becoming irreversible, are believed to increase as the duration of treatment and the cumulative dose of neuroleptics increase. However, the syndrome can develop, although less commonly, after relatively brief periods of treatmetnt at low doses. There is no known treatment for established cases of TD. The syndrome may remit, partially or completely, if neuroleptics treatment is withdrawn. Neuroleptics treatment it self, however, may suppress the signs and symptoms of TD thereby masking the underlying process.

Given these considerations, olanzapine should be prescribed in a manner that is most likely to minimize the risk of TD. As with any neuroleptics, olanzapine should be reserved for patients who appear to be receiving substantial benefit from the drug. In such patients the lowest effective dose and the shortest duration of treatment should be sought. The need for continued treatment should be reassessed periodically.

If signs or symptoms of TD appear in a patient on olanzapine, drug discontinuation should be considered. However, some patients may benefit from continued treatment with olanzapine despite the presence of the syndrome.

Precautions :

Potential Effect on Cognitive and Motor Performance : Because olanzapine may cause somnolence patients should be cautioned about operating hazardous machinery, including motor vehicles, until they are reasonably certain that olanzpaine therapy does not affect them adversely.

Hypotension and Syncope : As with other drugs that have high alpha-1 adrenergic receptor blocking activity, olanzapine may induce orthostatic hypotension, tachycardia, dizziness, and sometimes syncope especially at the initiation of treatment. In a clinical trial database of 2500 patients treated with olanzapine, syncope was reported in 0.6 percent (15/2500). The risk of orthostatic hypotension and syncope may be minimized by initiating therapy with 5 mg. A more gradual titration to the target dose should be considered if hypotension occurs. Olanzapine should be used with particular caution in patients with known cardiovascular disease, cerebrovascular disease, and conditions which would predispose patients to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medications).

Seizures : Conventional neuroleptics are known to lower seizure threshold. In clinical trials, seizures have occurred in a small number (0.9 percent 22/2500) of olanzapine-treated patients. There were confounding factors that may have contributed to the occurrence of seizures in many of these cases. Olanzapine should be used cautiously in patients who hove a history of seizures or have conditions associated with seizure or have a lowered seizure threshold.

Hepatic Function Indices : Transient, asymptomatic elevations of hepatic transaminases, ALT, AST have been seen occasionally, especially in early treatment. Caution should be exercised in patients with elevated ALT and/or AST, in patients with signs and symptoms of hepatic impairment, in patients with pre-existing conditions associated with limited hepatic functional reserve, and in patients who are being treated

with potentially hepatotoxic drugs. In the event of elevated ALT and/or AST during treatment, follow-up should be organized and dose reduction should be considered.

Hematologic Indices : As with other neuroleptics, caution should be exercised when using olanzapine in the following types of patients :

- in patient with low leukocyte and/or neurophil counts due to any reason;
- in patient with a history of drug-induced bone marrow depression/toxicity;
- in patient with bone marrow depression caused by concomitant illness, radiation therapy or chemotherapy; and
- in patient with hypereosinophilic conditions or with myeloproliferative disease.

In clinical studies, a significant number or patients with clozapine-related neutropenia or agranulocytosis histories received olanzapine without a recurrence.

Hyperprolactinemia : As with other drugs that block dopamine D_2, and/or serotonin 5-HT_2 receptors, olanzapine may elevate prolactin levels Elevations associated with olanzapine treatment are generally mild and may decline during continued administration.

Since tissue culture experiments indicate that approximately on third of human breast cancers are prolactin dependent *in vitro*, olanzapine should only be administered to patients with previously detected breast cancer if the benefits outweigh the potential risks. Caution should also be exercised when considering olanzapine treatment in patients with pituitary tumors. Possible manifestations associated with elevated prolactin levels are amenorrhea, galactorrhea and menogghagia.

As is common with compounds which stimulate prolactin release, the administration of olanzapine resulted in an increase in the incidence of mammary neoplasms in both rats and mice. The physiological differences between rats and humans with regard to prolactin make the clinical significance of these findings unclear. To date,

neither clinical nor epidemiological studies have shown an association between chronic administration of these drugs and mammary tumorigenesis.

Weight Gain : Olanzapine was associated with weight gain during clinical trials. Patients treated at higher doses had the greatest mean weight gain. However, a categorization of patients at baseline on the basis of body mass index (BMI) revealed a significantly greater effect in patients with low BMI compared to normal or overweight patients. Using pooled data from patients treated with olanzapine over the dosage range of 5 mg to 20 mg per day, weight gain tended to level off at 6 to 8 months of treatment with a mean gain of 5.4 kg.

Drug Interactions : Given the primary CNS effects of olanzapine caution should be used when it is taken in combination with other centrally-acting drugs and alcohol. As it exhibits in vitro dopamine antagonism, olanzapine may antagonize effects of levodopa and dopamine agonists. Because of its potential for inducing hypotension, olanzapine may enhance the effects of certain antihypertensive agents.

Pregnancy : There are no adequate an well-controlled studies in pregnant women. Patient should be advised to notify their physician if they become pregnant or intend to become pregnant during treatment with olanzapine. because human experience in pregnant females is limited this drug should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus.

Lactation : Olanzapine was excreted in milk of treated rats during lactation. It is not known if olanzapine is excreted in human milk. Patients should be advised not to breast feed an infant if they are taking olanzapine.

Geriatrics : The number of patients 65 years of age or over, with schizophrenia or related disorders, exposed to olanzapine, during clinical trials was limited. Caution should thus be exercised with the use of olanzapine in the elderly patient,

recognizing the more frequent hepatic, renal, central nervous system, and cardiovascular dysfunctions, and more frequent use of concomitant medication in this population.

Children : The safety and efficacy of olanzapine in children under the age of 18 years have not been proven.

Renal and Hepatic Impairment : Small single-dose clinical pharmacology studies, did not reveal any major alterations in olanzapine pharmacokinetics in subjects with renal or hepatic impairment. Given the limited clinical experience with olanzapine in patients with these conditions, caution should be exercised.

Symptoms and Treatment of Overdosage :

Experience with olanzapine in overdose is limited. In clinical trials, accidental or intentional acute overdose of olanzapine was identified in 67 patients. In the patient taking the largest identified amount, 300 mg, the only symptoms reported were drowsiness and slurred speech. Vital signs were usually within normal limits following overdoses.

Based on animal data, the predicted symptoms would reflect an exaggeration of the drug's known pharmacological actions. Symptoms may include somnolence, mydraisis, blurred vision, respiratory depression, hypotension, and possible extrapyramidal disturbances.

There is no specific antidote to olanzapine; therefore, appropriate supportive measures should be initiated. The possibility of multiple drug involvement should be considered.

In case of acute overdose establish and maintain an airway and ensure adequate oxygeneration and ventilation. The use of activated charcoal for overdose should be considered because the concomitant administration of activated charcoal was shown to

reduce the oral bioavailability of olanzapine by 50 percent to 60 percent. Gastric lavage may also be considered.

Hypotension and circulatory collapse should be treated with appropriate measures such as intravenous fluids and/or sympathomimetic agents such as norepinephrine. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias.[40]

Electroconvulsive Therapy (ECT)

History

Seizures produced by camphor were used to treat psychosis and mania in the 16th century by Phillipus Paracelsus and in the late 19th century by Leopold von Auenbrugger, W. Oliver, and Carl Weickhardt. The first modern application of convulsive therapy occurred in January 1934, when Ladislas J. von Meduna, who was apparently unaware of the earlier work, introduced camphor-induced seizures as a treatment for schizophrenia. Von Meduna thought that schizophrenia and epilepsy antagonize each other because catatonic and schizophrenic patients appear to be less psychotic after spontaneous seizures than before the seizures.

Convulsive therapy was initially associated with a 2 percent incidence of fractures of the extremities, a 17 percent incidence of dislocations, and a 50 percent incidence of compression fractures of the spine. Those risks were eliminated when psychiatrist A.E. Bennett introduced muscle relaxants to the procedure in 1940. Bennett used curare, which had been encountered by Sir Walter Raleigh in the 16th century and which was shown to block the neuromuscular junction by physiologist Claude Bernard in 1849.

The use of electricity to induced seizures was introduced in April 1938 by Ugo Creletti and Lucio Bini and was imported to the United States by Lothar Kalinowsky and others in 1939. Bini originally thought that electrical induction may be dangerous when a number of dogs died in early experiments and when he heard that electricity is used in slaughterhouses to dill animals. However, he realized that it is passing the current through the heart that is fatal in the laboratory. Passing an electric current through the head is not harmful in itself and is used in slaughterhouses only to render animals unconscious, so that they can be killed painlessly, That history is sometimes misquoted by anti-ECT activists to show the dangerousness of ECT.

As experience with ECT grew, clinicians found it to be more effective for mood disorders than for schizophrenia, and mood disorders remain the primary indications for ECT. The use of ECT declined after the introduction of neuroleptics and antidepressants, but its use has grown in recent years. An estimated 50,000 to 100,000 patients a year now receive ECT.[41]

Mechanisms of Action

Theoretical Issues

The intensity of the current relative to the area of the brain through which it passes may be related to the neurobiological effects of ECT. The intensity or dose of electricity is measured in units of *charge* (milliampere-seconds or millicoulombs) or *energy* (watt-seconds or joules). In the human body, resistance to the passage of electricity is called *impedence*, which is for practical purposes equivalent to electrical resistance in other models. Impedence is determined by the quality of the contact between the electrodes and the skin and the nature of the tissue; the brain has low impedence, and the skull has high impedence. Dealing with impedence is a common technical problem in ECT.

ECT machines keep current, voltage, or energy at constant levels by varying other parameters. Because of the relation between current, voltage, and impedence summarized by Ohm's law (Figure 2), *constant-current* devices increase the voltage as impedence increases (for example: with poor skin contact). When the voltage reaches a preset limit that prevents skin burns, it can no longer drive sufficient current to produce a seizure. *Constant-voltage* devices decrease current in response to higher impedence. With *constant-energy* devices, energy is maintained at a predetermined level by varying the duration of the stimulus; The duration of stimulation decreases with increasing impedence because energy is proportional to the product of resistance and the time of current delivery, and one must decrease if the other increases.

Figure 2 : Ohm's law

$$E = IR$$

$$I = E / R$$

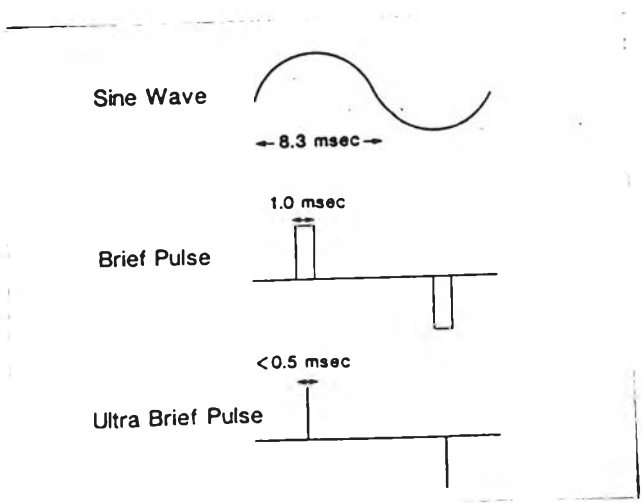
E = voltage

I = current

R = resistance (impedence)

Types of Electrical Stimulation : Electrical stimuli that are used to produce seizures consist of bidirectional cycles of one positive and one negative wave per cycle. The sine waveform of stimulus (Figure 3) is now considered obsolete because of its inefficiency. During the initial portion of each phase, the stimulus is below the level of intensity necessary to produce a seizure (*seizure threshold*); after the energy peak, stimulation is applied to refractory neuron, producing side effects but no more efficacy. The *brief pulse* stimulus (Figure 3) is a bidirectional square wave that rapidly reaches peak intensity and then abates, avoiding initial subthreshold stimulation and continued stimulation after the neurons become refractory. It is easier to exceed the seizure threshold with brief pulse stimulation than with sine wave stimulation and with 2 m/sec than with 1 m/sec brief pulse stimuli. However, very long pulses may be less efficient than shorter pulses, and ultrabrief pulses may be less efficient than shorter pulses, and ultrabrief pulses (Figure 3) are less effective than brief pulses.[42]

Figure 3 : Stimulus Waveforms.



Effects on Electroencephalogram : ECT produces a generalized central seizure that spreads through the cortex and ends with a period of electrical silence (*postictal suppression*) lasting up to 90 seconds. Postictal suppression is followed by high-voltage delta waves and then theta waves, with a return to the preseizure electroencephalogram (EEG) pattern in 20 to 30 minutes. In addition to the short-term seizure discharge and its aftermath, the interictal EEG tends to become slower and its amplitude greater as additional ECT treatments are administered at a rate of at least one a week. The EEG returns to normal 1 to 12 months after treatment ends.

Effects on Cerebral Blood Flow : During artificially induced seizures, there are increases in cerebral blood flow, permeability of the blood-brain barrier, metabolic rate, and the consumption of oxygen and glucose in the neocortex and the hippocampus. Enhanced delivery of oxygen is sufficient to meet the increased metabolic demand, and the brain is never short of oxygen if the patient is adequately oxygenated. Postictally, a global decrease in cerebral blood flow, especially in the frontal cortex, may be more pronounced in responders than in nonresponders.[42]

Mechanisms of Action of ECT

In reviewing any therapeutic technique the two most fundamental concerns are safety and efficacy. Since most clinicians are uncomfortable with any technique whose mechanism of action is unknown, some anxiety occurs when ECT is considered. Older literature has suggested that the efficacy of ECT was dependent on the actual physical convulsion yet may produce a highly beneficial result. Furthermore, earlier thinking about ECT suggested that the beneficial effect was connected with the induction of memory loss and confusion, which somehow allowed for the patient's recovery. Again, with the application of newer techniques such as the administration of much smaller amounts of electrical energy to the nondominant hemisphere, a course of several treatments may be administered with little or no confusion or memory change but with a sizable therapeutic benefit.

Although a variety of techniques of ECT have been associated with a therapeutic response, the only finding that appears absolutely necessary is the development of a generalized electrical seizure within the brain. One thing that makes the response to ECT puzzling, as various mechanisms of action are considered, is the finding that although depression is the condition most responsive to ECT there may also be a favorable therapeutic response in manic patients and in some individuals with schizophrenia, wherein presumably different mechanisms of action must be invoked.

There are many known neurotransmitters, and a larger number which are still either unknown or poorly understood. Most of the data thus far available regarding the effects of ECT on neurotransmitters are derived from animal studies. Effects on various transmitters appear contradictory at times, although this may help to explain what appear to be opposite results when ECT may benefit either depression or mania. Some studies have suggested that following a series of electrically induced seizures in rats, there is increased turnover of norepinephrine and possibly a net increases in both brain level and synthesis of norepinephrine. MHPG (3-methoxy 4-hydroxyphenyl-glycol) levels in the urine of depressed patients have been reported to increase following a series of ECT , presumably suggesting increase in norepinephrine turnover associated with improvement in mood.

Brain levels and turnover of serotonin increase in animals following a series of electrically induced seizures. Abnormally low CSF levels of the serotonin metabolite 5-hydroxyindolacetic acid (5-HIAA) may increase to ward normal with ECT-induced remission in depression. Electroconvulsive shocks administered to rats dramatically increase dopamine levels in the striatum, and electroconvulsive therapy has a beneficial effect in Parkinson's disease, suggesting that increased brain dopamine concentrations may occur with ECT. Thus there is experimental evidence of enhancement of at least three neurotransmitters thought to be involved in the mechanism of depression by electroconvulsive therapy, yet there is not enough evidence to state with certainty that these mechanism explain the beneficial effects of ECT. It is intriguing to postulate a more important role of dopamine deficiency states in some forms of depression to explain the

therapeutic benefit of ECT in some patients who are unresponsive to conventional antidepressants. In humans electroconvulsive therapy has been found to activate the hypothalamic-pituitary-adrenal axis, resulting in the release of beta-endorphin. There are conflicting data in the literature regarding changes in the serum levels of the catecholamine metabolites MHPG and HVA following ECT; on the other hand, most studies have confirmed ECT-induced increases of serum prolactin concentration proportional to seizure duration.

In animal studies, ECT, like antidepressant drugs, has led to down regulation of both beta-and alpha-adrenergic receptors as well as Serotonin 5-HT_2 receptors. There is evidence of a generalized release of acetylcholine throughout the brain during the course of ECT and of increases in spinal fluid acetylcholine and choline levels associate with the ECT. Although it may be difficult to correlate increased acetylcholine levels with an improvement in mood in depressed patients, this finding is interesting since the administration of acetylcholine precursors to manic patients may improve the symptoms of mania. Perhaps similar or related changes may account for some of the favorable observations of ECT in schizophrenia. The extracellular concentration of GABA is increased (though GABA synthesis is decreased) following ECT in animals. The old idea of "brain scrambling" as a mechanism for ECT would seem to be far behind our sophisticated age of neurochemistry and psychopharmacology, yet more work is needed to correlate neurochemistry with observed therapeutic responses.[43]

Indications

Referrals for ECT are based upon a combination of factors, including the patient's diagnosis, nature are severity of symptomatology, treatment history, consideration of anticipated risks and benefits of viable treatment options, and patient preference. At present there are no diagnoses which should automatically lead to treatment with ECT. In most cases ECT is used following treatment failure on psychotropic agents, although specific criteria do exist for use of ECT as a first-line treatment

Primary Use of ECT : Situations where ECT may be used prior to a trial of psychotropic agents include, but are not necessarily limited to, the following:

a) where a need for rapid, definitive response exists on either medical or psychiatric grounds; or
b) when the risks of other treatments outweigh the risks of ECT; or
c) when a history of poor drug response and/or good ECT response exists for previous episodes of the illness; or
d) patient preference.

Secondary Use of ECT : In other situations, a trial of an alternative therapy should be considered prior to referral for ECT. Subsequent referral for ECT should be based on at least one of the following:

a) treatment failure (taking into account issues such as choice of agent, dosage, and duration of trial);
b) adverse effects which are unavoidable and which are deemed less likely and/or less severe with ECT;
c) deterioration of the patient's condition such that criterion of primary use of ECT is met.

Major Diagnostic Indications

Diagnoses for which either compelling data are present for efficacy of ECT, or a strong consensus exists in the field supporting such use.

Major Depression :

a) ECT is an effective treatment for all subtypes of unipolar major depression, including major depression, recurrent.

b) ECT is an effective treatment for all subtypes of bipolar major depression, including bipolar disorder, depressed; bipolar disorder, mixed; and bipolar disorder, not otherwise specified.

Mania : ECT is an effective treatment for all subtypes of mania, including bipolar disorder, mania; bipolar disorder, mixed; and bipolar disorder, not otherwise specified.

Schizophrenia and Other Functional Psychoses :

a) ECT is an effective treatment for psychotic schizophrenic exacerbations in the following situations:

1. catatonia; or
2. when affective symptomatology is prominent; or
3. when there is a history of a favorable response to ECT.

b) ECT is effective in related psychotic disorders, notably schizophreniform disorder and schizoaffective disorder. ECT may also be useful in patients with atypical psychosis when the clinical features are similar to those of other major diagnostic indications.

Other Diagnostic Indications

Diagnoses for which efficacy data for ECT are only suggestive, or where only a partial consensus exists in the field supporting its use. In such cases, ECT should be recommended only after standard treatment alternatives have been considered as a primary intervention. The existence of such indications, however, should not deter the use of ECT for treatment of a concurrent major diagnostic indication.

Mental Disorders : Although ECT has sometimes been of assistance in the management of mental disorders other than those described above, such usage is not adequately substantiated and should be carefully justified in the clinical record on a case-by-case basis.

Organic Mental Syndromes : ECT may be effective in the management of severe organic affective and psychotic conditions displaying symptomatology similar to functional diagnoses, or in treating delirium of various etiologies, including toxin and metabolic.

Medical Disorders :

a) The neurobiologic effects associated with induced generalized seizure activity may be of benefit in treating a small number of medical disorders.

b) Such conditions include, but are not limited to :

1. catatonia secondary to medical conditions
2. hypopituitarism
3. intractable seizure disorder
4. neuroleptic malignant syndrome
5. Parkinson's disease (particularly with the"on-off" phenomenon)[44]

Contraindications

There are no absolute contraindications to ECT. However, certain conditions are associated with substantial risk.

Space-occupying lesion : The major risk of ECT to patients with space-occupying lesions is that the increased cerebral blood flow and permeability of the blood-brain barrier to water associated with the treatment can produce excessive edema around to lesion, leading to herniation. Early reports of fatalities associated with ECT contained a significant proportion of patients with brain tumors, but the recent literature contains reports of patients with brain tumors and other intracranial lesions diagnosed in advance or retrospectively who had no adverse reactions. However, the lesions have been small, asymptomatic, and not associated with increased intracranial pressure, and negative experiences may be less likely to be reported than are positive experiences. Aggressive treatment of hypertension during ECT and the prophylactic use of dexamethasone (Decadron) may decrease the risk in patients with space-occupying lesions.

High intracranial pressure : The elevation of intracranial pressure that occurs during ECT can be expected to aggravate preexisting high intracranial pressure. A report

exists of one patient with high intracranial pressure but no mass lesion who had no adverse reactions to ECT, but experience is too limited to draw any specific conclusions.

Intracerebral bleeding : Increases in blood pressure and cerebral blood flow can place patients with unstable aneurysms, evolving hemorrhagic cerebrovascular accidents, or vascular malformations at risk of rebleeding, especially with multiple monitored ECT, but experience is too limited to draw any specific conclusions.

Recent myocardial infarction : If cardiac function is unstable, the patient faces a risk of reinfarction, heart failure, ventricular arrhythmia, and cardiac rupture caused by the cardiovascular changes of ECT. The risk is greatest during the first 10 days after infarction and resolves completely after three months. ECT is usually deferred during that periods; if delay is not possible, maximal oxygenation is provided, and antihypertensives and antiarrhythmics are administered.

Miscellaneous conditions : Several other situations have been found to require careful blood pressure control or anesthetic management during ECT. They include retinal detachment, pheochromocytoma, and high anesthesia risk.[45]

Adverse Effects

Physicians administering ECT should be aware of the principal adverse effects which may accompany its use. The nature, likelihood, and persistence of adverse effects should be considered on a case-by-case basis in the decision to recommend ECT and in obtaining informed consent. Also, efforts should be made to minimize adverse effects by appropriate modifications in ECT technique and the use of adjunctive medications.

Cognitive Dysfunction : Orientation and memory function should be assessed prior to ECT and periodically throughout the ECT course to detect and monitor the presence of

ECT-related cognitive dysfunction. This assessment should attend to patient self-reports of memory difficulty.

If a patient develops severe cognitive side effects, the physician administering ECT should review the case and take appropriate action. The contributions of medications, ECT technique, and spacing of treatments should be reviewed. Potential treatment modifications include a change from bilateral to unilateral right electrode placement, decreasing the intensity of electrical stimulation, increasing the time interval between treatments, and/or altering the dosage of medications, or, if necessary, terminating the treatment course.

Cardiovascular Dysfunction : The electrocardiogram (ECG) and vital signs (blood pressure, pulse, and respiration) should be monitored during each ECT treatment in order to detect cardiac arrythmias and hypertension.

Each facility should be prepared to manage the cardiovascular complications known to be associated with ECT. Personnel, supplies, and equipment necessary to perform such a task should be readily available.

Prolonged Apnea : Resources for maintaining an airway for an extended period, including intubation, should be available in the treatment room

Treatment Emergent Mania : Rare occurrences where patients switch from depressive or affectively mixed states into hypomania or mania during a course of ECT should be distinguished from organic euphoria. Treatment strategies include continuation of ECT, delay of ECT and observation of the patient, and termination of the ECT course followed by pharmacotherapy.

Adverse Subjective Reactions : Apprehension and/or fear of ECT by patients or their families should be addressed both during the informed consent procedure, and

throughout the ECT course. The discussion of such concerns with the attending physician and/or members of the ECT treatment team is encouraged, and, where indicated, treatment procedures should be modified to alleviate such problems.

Other Adverse Effects : Headache, nausea, and muscle ache or soreness during the first few hours following seizure induction are common. Such occurrences warrant symptomatic treatment. When such effects are recurrent or particularly bothersome, prophylaxis should be considered.[46]

Techniques

Informed Consent : A 1990 report of the American Psychiatric Association find that patients undergoing any procedure understand less than half of the information contained in a consent form and tend to attribute the decision for the procedure to their physicians. The trend is no more marked in psychiatric patients than in medical patients, but it indicates the importance of making sure that any patient offered ECT understands the illness, the exact nature of the treatment, why ECT is being recommended, the potential side effects and benefits, alternative treatments, and the consequences of refusing ECT.

Pretreatment Evaluation : Before ECT, patients receive a psychiatric, medical, neurological, and anesthesiological evaluation. An electrocardiogram, complete blood count, and electrolyte determinations are recommended by most experts, as is a dental examination for geriatric patients to determine whether the anesthetist will need to adjust the procedure for dentures or problem teeth. Special tests, such as an EEG and brain-imaging studies, are given only if the clinical examination suggests an abnormality. The routine use of skeletal muscle relaxant has eliminated the risk of bone damage and with it the need for pretreatment spine X-rays unless spinal disease is suspected.

Patient Preparation : The patient is given nothing to eat or drink for six hours before an ECT treatment. In the treatment area the patient's mouth is checked for foreign

bodies, and an intravenous line is inserted in an arm or hand vein. Just before delivery of the electrical stimulus, a bite block is inserted, against which the patient's jaw is held to protect the teeth. Oxygenation is maintained with 5 liters a minute of 100 percent oxygen from the beginning of anesthesia until resumption of spontaneous breathing. Equipment for emergency airway management is kept available but is not used during routine treatment.

Medication During ECT : A number of medications are regularly administered during ECT. Including medications used to treat the complications of ECT are discussed.

Muscarinic anticholinergic drugs are used to dry secretions and to block vagally mediated bradyarrhythmias and asystole. No controlled studies demonstrate the need for routine use of the drugs, but they are thought to be indicated for patients taking sympathetic blocking drugs and when transient cardiac slowing may be dangerous. The intravenous route provides the most reliable absorption. Atropine (Lomotil) is the most commonly used anticholinergic during ECT. Glycopyrrolate (Robinul) is less likely than atropine to cross the blood-brain barrier but may be less efficient in protecting the cardiac rate and rhythm and has not been shown to produce less cognitive dysfunction or nausea.

Short-acting *anesthetics* are essential to prevent discomfort associated with ECT. Methohexital (Brevitol) is most widely used because it is associated with a lower incidence of postictal arrhythmias than thiopental (Pentothal); however, arrhythmias reported with thiopental may have been a result of inadequate ventilation, resulting in hypercapnia and not the drug itself. Etomidate is unlike barbiturate anesthetics in that it does not raise the seizure threshold and, therefore, may be useful with elderly patients in whom it is difficult to obtain a seizure. In one study etomidate appeared to prolong seizure duration. Ketamine (Ketalar) does not raise the seizure threshold and can be administered intramuscularly to patients in whom it becomes impossible to maintain an intravenous line, but the drug frequently causes postictal psychosis and altered states of consciousness. Alfentanil (Alfenta) is sometimes coadministered with methohexital to allow a lower than

usual dose of barbiturate and, therefore, less interference with seizures, but the drug may cause nausea.

Skeletal muscle relaxants, which are used to block the motor convulsion, are administered as soon as the patient is unconscious with an airway inserted. The goal is profound relaxation but not necessarily total paralysis unless the patient has osteoporosis, a history of spinal injury, or a pacemaker. The adequacy of relaxation is tested by observing the disappearance of fasciculations in the small muscles of the feet or by attempting to produce muscle contractions with a peripheral nerve stimulator. The most commonly used muscle relaxant is succinylcholine (Anectine). Tubocurarine is sometimes administered just before succinylcholine to prevent myalgias and increases in serum concentrations of potassium and muscle enzymes caused by muscle fasciculation. In cases of pseudocholinesterase deficiency, a condition so rare that it is not necessary to screen for it routinely, atracurium (Tracrium) or curare are alternatives to succinylcholine.

Electrode Placement : Two types of electrode placement are available. In bilateral ECT the electrodes are placed on each side of the head in frontotemporal location about one inch above the midpoint of a line from the tragus of the ear to the external canthus of the eye. Bilateral placement is often recommended as the first approach for patients with conditions listed in Table 4. Otherwise, bilateral ECT is generally used only if unilateral ECT is ineffective.

Table 4 : Indications for Bilateral ECT[47]

Severe depressive disorder
Agitation
Immediate suicide risk
Major depressive disorder with psychotic features
Manic episode
Catatonic stupor
Treatment-resistant schizophrenia
Parkinson's disease
Concomitant medical problem requiring few anesthetic exposures

Because the right hemisphere is nondominant for language, even in most left-handed persons, both electrodes for unilateral ECT are usually placed on the right side of the head . The most common location is the d'Elia placement, in which one electrode is in the standard frontotemporal position and the other is one inch ipsilateral to the vertex of the skull. Unilateral ECT is recommended as the initial treatment in many uncomplicated situations, with a change to bilateral placement recommended if the patient shows no response after four to six treatments.

Stimulus Intensity : Specialists often recommend that the electrical stimulus be delivered at an intensity 50 percent to 200 percent (three times) the seizure threshold. Higher stimulus intensity increases the effectiveness of right unilateral , but not necessarily bilateral, ECT. Finding the appropriate stimulus dosage is complicated by a 40-fold variability in the seizure threshold from one person to the next and a 25 to 200 percent increase in the seizure threshold as treatment progresses. In addition, the seizure threshold is higher for men and for elderly patients than for women and young patients, whereas it may be lower in manic than in depressed patients. Seizure threshold is higher for bilateral than right unilateral ECT and increases with increased head size. The same stimulus intensity, therefore, may be excessive for one patient and subtherapeutic for another. Some clinicians determine the appropriate dosage by beginning with stimulation that is likely to be subconvulsive and then increasing the stimulus intensity to the seizure threshold. The next stimulation is set at 100 percent greater than threshold for unilateral ECT and 50 percent above threshold for bilateral ECT, with further adjustments as indicated clinically.

Seizure Monitoring : Seizures that do not generalize bilaterally or that are less than 25 seconds in duration are not thought to be effective. However, that seizure duration criterion has been questioned because it is not based on prospective research. EEG monitoring is the most accurate way of monitoring seizure duration. Another approach is to inflate a blood pressure cuff 10 mm above the anticipated systolic blood pressure during a seizure to prevent succinylcholine from reaching that limb. The cuff should be on the

same side as the electrodes with unilateral ECT to observe contralateral cortical spread of the seizure. Because the cerebral seizure often lasts longer than its motor manifestations, the longest duration of motor activity is counted.

Seizure generalization cannot be measured directly but may be inferred from the degree of postictal EEG suppression, which reflects the number of neurons that are refractory. Other possible measures of adequate seizure generalization may be interictal EEG slowing, a fivefold to tenfold increase in serum prolactin concentration that peaks about 20 minutes after a seizure, the persistence of ECT-induced tachycardia, and a positive correlation between various measures of seizure duration.

Treatment Course : ECT is usually administered two to three times a week. There is no difference in efficacy between those approaches, but the twice-weekly schedule produces less cumulative memory loss than a thrice-weekly schedule and may allow more time for the full effect of each seizure to develop. Although the twice-weekly schedule may be preferable to the patient, third-party payers anxious for a quicker and therefore cheaper response may be reluctant to cover that schedule, especially if the patient is hospitalized. Increasing use of outpatient ECT for patients who are not in acute danger may be a way around this problem. The average course of ECT for melancholia is 6 to 12 treatments, but some patients require as many as 20; a hypothesis that a therapeutic range of total seizure times exists was not supported by subsequent research. The duration of each seizure at least beyond the minimum noted earlier also does not predict treatment outcome. The number of ECT treatments reported to be effective for mania has ranged from 8 to 20, and schizophrenia may require 17 or more treatments. Catatonia, delirium, and psychogenic confusional states often respond to one to four treatments.

Clinical experience suggests that ECT be continued until the patient has shown a maximal response; no evidence indicates that administering one or two additional treatments results in a better outcome. Indeed, increased confusion from the additional treatments may produce clinical deterioration. If a patient responds to a few treatments,

further ECT is withheld, and the patient is observed for evidence of the need for more treatment. ECT is discontinued in patients who have had a partial but substantial improvement but show no change after two more treatments and in patients who have not responded at all after 6 to 10 treatments with at least some bilateral administration.

Multiple Monitored ECT : Multiple monitored ECT consists of multiple seizures induced during the same session. More than two seizures at a time may produce so much confusion that the patient cannot tolerate further therapy. However, some evidence from clinical observations indicates that inducing two bilateral seizures within one or two minutes of each other to allow for the refractory period may lead to more rapid improvement in severely ill patients, manic patients, and patients with a high anesthetic risk who should have the fewest possible anesthesias. Confusion is greater with multiple monitored ECT than with the usual ECT, but the confusion resolves by the end of therapy.

ECT Resistance : Just as patients who do not respond to medications may have received inadequate drug dosages, insufficient stimulus dosage may contribute to resistance to ECT. Some patients may require stimulus intensities 200 to 300 percent above the seizure threshold, which itself may have increased over the course of ECT. If unilateral ECT at adequate stimulus doses had been ineffective, bilateral ECT may be more successful. Some patients begin to respond only after 10 to 15 bilateral treatments and require a total of 16 to 24 treatments for a complete response. Some patients respond to one or more additional courses of ECT. It has been suggested but not demonstrated in formal research that some ECT-resistant patients respond to subsequent medication trials or to multiple monitored ECT.

Continuation and Maintenance Therapy : Although ECT is highly effective as short-term treatment for depression, 50 to 70 percent of nonpsychotically depressed patients and up to 95 percent of psychotically depressed patients relapse, at least one half to four fifths of them in the first two to four months after the completion of therapy. The relapse rate is reduced to about 20 percent in patients maintained after ECT on antidepressants or

lithium. Psychotically depressed patients appear to require the continuation of therapeutic dosage of neuroleptics, as well as antidepressants or lithium.

Continuation ECT is indicated for patients who do not tolerate or respond to continuation medications or who prefer ECT. After remission, continuation ECT treatment are administered at weekly intervals, and the frequency of treatment is gradually decreased to once a month. Treatment is provided more frequently than that to patients who are at high risk or relapse because of , for instance, an incomplete response or a recurrent course.

Prophylactic ECT that is continued more than six months after remission is called maintenance ECT. Maintenance ECT administered once a week to once a month or less often than that decreases the frequency and the duration of depressive relapses, although studies of maintenance ECT have been confounded by the concurrent use of medications. Treatment has been continued for periods of four or six months or five years or longer; some patients apparently require indefinite maintenance ECT.[47]

Review of Related Studies

Tollefson GD. and associates,[48] studied the comparison of olanzapine and haloperidol in the treatment of schizophrenia by conducting an international collaborative, multicenter, 6-weeks, double-blind trial. A total of 1,996 patients are randomly assigned to treatment with olanzapine (n=1,336) or haloperidol (n=660) and being assess by Brief Psychiatric Rating Scale (BPRS), comparison of the mean change in positive and negative symptoms, comorbid depression, extrapyramidal symptoms, and overall drug safety. As a result, olanzapine shows a superior and broader spectrum of efficacy in the treatment of schizophrenic psychopathology, with a substantially more favorable safety profile, than haloperidol.

Due to the fact that a comparison of typical neuroleptic and clozapine produces a unique pattern of Fos-like immunoreactive neurons in the rat forebrain. Robertson GS. and associates,[59] then, examined the ability of olanzapine to increase the number of Fos-like immunoreactive neurons in the striatum, nucleus accumbens, lateral septal nucleus, and prefrontal cortex by using olanzapine (5, 10 mg/day) which produced dose-dependent increases in the number of Fos-positive neurons in the nucleus accumbens and lateral septal nucleus, important components of the limbic system that may mediate some of the therapeutic actions of neuroleptics. In conclusions, olanzapine's actions in the medial prefrontal cortex may be predictive of a clozapine-like profile with respect to actions on negative symptoms in schizophrenia.

From the study of Gallhofer B. and associates,[49] the cognitive dysfunction in schizophrenia was being compare between atypical neuroleptics and typical neuroleptics. To determine the effect on cognition, the maze tasks were used. As a result, patients on atypical neuroleptic showed better performance on the maze tasks than untreated patients or patients taking typical neuroleptics. In particular, they were better able to maintain motor coordination while they focused on the more complex "frontal" maze tasks which required sequencing and planning.

The subjective quality of life in schizophrenic patients using typical neuroleptics were being compare with schizophrenic patients using atypical neuroleptics by Franz M. and associates.[50] A standardised quality of life were being interview with 33 patients on atypical neuroleptics and 31 matched patients on typical neuroleptics. As a result, atypical neuroleptics group had significantly higher scores in general quality of life as well as in different life domains : physical well-being, social life, and everyday life.

Beasley CM Jr. and associates [51] have compared two doses of olanzapine (1mg/day; 10mg/day) with placebo in the treatment of 152 schizophrenic patients with Brief Psychiatric Rating Scale's total score of 24 or more. The Positive and Negative Syndrome Scale (PANSS) and the Brief Psychiatric Rating Scale (BPRS) was being use to assess. As a result, olanzapine at 10mg/day was statisticallly significantly superior to placebo, both in positive and negative symptom and at the end point, the incidence of patients with elevated prolactin values did not differ statistically significantly between placebo-treated and olanzapine at 10mg/day treated patients. As for olanzapine at 1mg/day, it was clinically comparable to placebo in all efficacy comparisons.

Tollefson GD. and associates,[52] compared the incidence of tardive dyskinesia among patients receiving olanzapine and those receiving the typical neuroleptic. Due to this study, their findings support an atypical extrapyramidal symptom profile and the potential of a significantly lower risk of tardive dyskinesia with olanzapine than with typical neuroleptic among patients requiring maintenance neuroleptic treatment.

Hamilton SH. and associates,[53] have done a double-blind study to evaluated the impact of treatment with olanzapine compared with haloperidol, and placebo on improvements in symptomatology and quality of life in schizophrenic patients. A total of 335 patients was randomized to each treatment groups; 3 various doses of olanzapine, haloperidol, and placebo. The efficacy measures included the Brief Psychiatric Rating Scale, scale for assessment of negative symptoms summary, and clinical global impressions severity scores, and quality of life scale. After 24 weeks of therapy showed

that olanzapine was significantly superior to placebo in reducing clinical severity and significantly superior to haloperidol in reducing negative symptoms in patients responding to acute treatment. Furthermore, improvement in quality of life was observed in olanzapine-treated responders.

Beasley and colleagues[68] conducted primary clinical trial safety database included 2500 patients treated with olanzapine (atypical neuroleptic), 810 with haloperidol (typical neuroleptic), and 236 with placebo. The significant side effects included somnolence, weight gain , and asymptomatic transaminase for atypical neuroleptics. In addition, pharmacological properties and therapeutic efficacy in the management of schizophrenia and related psychoses. And olanzapine was associated with significantly fewer side effect of movement disorder. The only events recorded more frequently during olanzapine than during haloperidol therapy were weight gain, dry mouth and increased appetite.

Fink and associates [54] have reviewed 122 studies, published between the year 1938 to 1994, on the role of ECT in schizophrenia. This treatment was found to be an effective treatment for psychosis. It is particularly applicable in patients with first-break episodes, especially those marked by excitement, overactivity, delusions, or delirium; in young patients, to avoid the debilitating effects of chronic illness; and in patients with syndromes characterized by catatonia, positive symptoms of psychosis, or schizoaffective features.

Some experts contend that schizophrenic patients typically require 10-20 treatments of ECT, and that negative symptom manifestations may require even more treatments. In supportive to this idea, Baker and associates [55] reported superior result in chronic schizophrenia after 20 treatments relative to 12 treatments.

In 1991, Devanand and associates [56] compared a group of eight patients who each had received more than 100 bilateral, modified sine wave ECT treatments, with a

matched group of patient who had never received ECT. They found no difference between the groups in neuropsychological measures, suggesting that patients given many courses of ECT treatment do not manifest measurable cognitive impairment in long-term follow-up.

Aoba and associates [57] found that plasma and red blood cell level of haloperidol increased transiently by about 100 percent immediately after ECT in schizophrenic patients.

Abraham KR. and Kulhara P.,[58] investigated in a double-blind trial on 22 schizophrenic patients receiving trifluoperazine and were randomly allocated to received eight real or eight simulated ECT. As a result, the group with real ECT showed significant improvement in the first eight weeks. However, the groups showed no significant differences from that time onward.

According to prospective clinical trials comparing combination treatment with single treatment, Smith and associates [20] reported that ECT combined with CPZ (chlorpromazine) had a higher discharge rate and a lower rehospitalization rate than CPZ alone.

Hafner and Holme[66] conducted a study of electroconvulsive therapy in a psychiatric intensive care unit. All patients were very severely disturbed and had failed to respond to medication given at highest levels judge to be safe. Response to electroconvulsive therapy was generally rapid and marked, which then , allowing substantial reductions in medication. Both of there experiments have described the efficiency of electroconvulsive therapy (ECT) to be rapid and marked for a certain period of time.

Safferman and Munne (1992)[65] summarized a case of patient with schiaophmeia who had have a response to clozapine (atypical neuroleptics) alone, and while on clozapine was virtually symptom free for 5 months. However, her psychosis recurred and

did not improve despite continuation of clozapine (900mg./day). With eight bilateral electroconvulsive therapy (ECT) treatments, concurrent with a reduced clozapine dose (400mg/day), she manifested marked improvement.

From the above previous studies, both ECT and neuroleptic drugs can be beneficial and harmful at the same time. The method of combination treatment between ECT and neuroleptic drugs seems to be the most effective for schizophrenic patients. There were only case reports on combination of ECT and atypical neuroleptics therefore, comparison of ECT combined with atypical neuroleptic versus atypical neuroleptic in schizophrenic patients seems to be an interesting topic for a research.