Preventing Clinical Deterioration in the Course of Schizophrenia: The Potential for Neuroprotection

This ACADEMIC HIGHLIGHTS section of The Journal of Clinical Psychiatry *presents the highlights from the teleconference series "Preventing Clinical Deterioration in the Course of Schizophrenia: The Potential for Neuroprotection," which was held in January and February 2006, was independently developed by the CME Institute of Physicians Postgraduate Press, Inc. and i3 DLN, and was supported by an educational grant from Eli Lilly and Company. This report was prepared by the CME Institute of Physicians Postgraduate Press, Inc.*

The teleconferences were chaired by ***Jeffrey A. Lieberman****, M.D., Columbia University College of Physicians and Surgeons and New York State Psychiatric Institute, New York. The faculty were* ***L. Fredrik Jarskog****, M.D., Department of Psychiatry, University of North Carolina School of Medicine, Chapel Hill; and* ***Dolores Malaspina****, M.D., M.S.P.H., Columbia University College of Physicians and Surgeons and New York State Psychiatric Institute, New York.*

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Natural History and Clinical Course of Schizophrenia

Jeffrey A. Lieberman, M.D., opened with a brief overview of the natural history of schizophrenia. When Emil Kraepelin[1] initially distinguished dementia praecox, which later came to be known as schizophrenia, from general insanity, he did so based not on patients' symptoms or on any particular aspect of the clinical presentation but on the longitudinal course of the illness, particularly the clinical deterioration that was noticed in patients. Patients with schizophrenia in the early part of the twentieth century, when Kraepelin was performing his research, had no treatment available to them and thus were forced to suffer the consequences of their illness. These people were able to function at some level—they could walk, talk, and eat—but they were not able to manage their way in the world, live independently, or function in any gainful way. Thus, they had to be supervised and maintained in an institution since they were residually symptomatic and functionally disabled as a result of the schizophrenia. This was the plight of patients with schizophrenia for the entire course of history until the latter part of the 20th century, when the first effective antipsychotic medications were introduced.

Dr. Lieberman explained that the natural history of schizophrenia has been mapped out over a period of more than a century by psychiatrists and researchers, like Kraepelin, who have observed the longitudinal course of the illness. Although a wide degree of variability exists in the presentation of the illness and the way in which it affects individual patients, the illness typically conforms to a fairly consistent natural history and clinical course. This course can be described in the context of specific clinical stages, from premorbid to prodromal onset/progression, deterioration, and finally, the chronic/residual stage (Figure 1).[2]

Clinical Deterioration

Even though schizophrenia may have its origins in etiologic factors that occur in early development, the illness does not express itself overtly until the person reaches the vulnerable age of risk, which is almost always after puberty and usually during mid-to-late adolescence or early adulthood. Dr. Lieberman explained that when schizophrenia begins to occur, it generally does so gradually in the form of nonspecific early warning signs called *prodromal symptoms*. Eventually, as these prodromal symptoms worsen or persist, they evolve into the symptoms that define the illness—the characteristic "psychosis." When people experience symptoms that are sufficiently severe as to be distressing or disabling enough to prompt them or their family to take them to a physician to seek treatment, they can be diagnosed as having schizophrenia. The person is then said to have experienced his or her first episode of illness.

According to Dr. Lieberman, most patients in their first episode of illness respond to treatment, achieving symptom remission and sometimes even recovery, but the vast majority of

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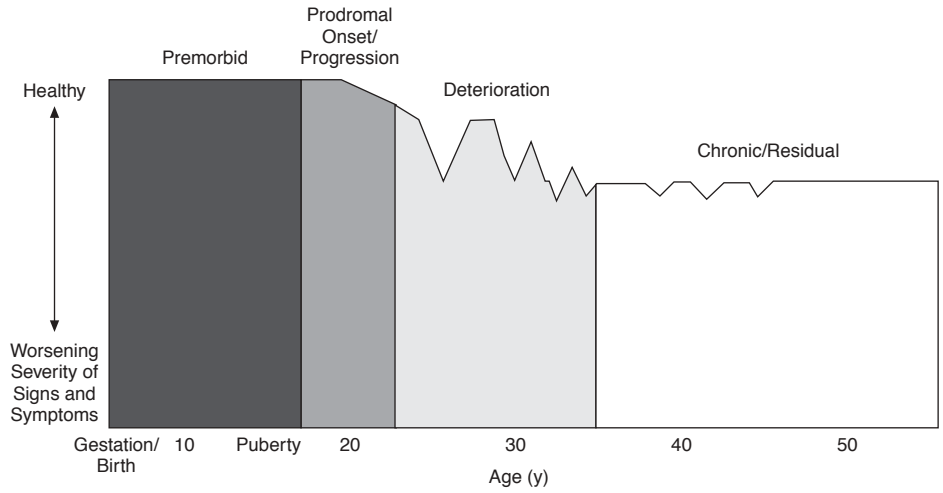
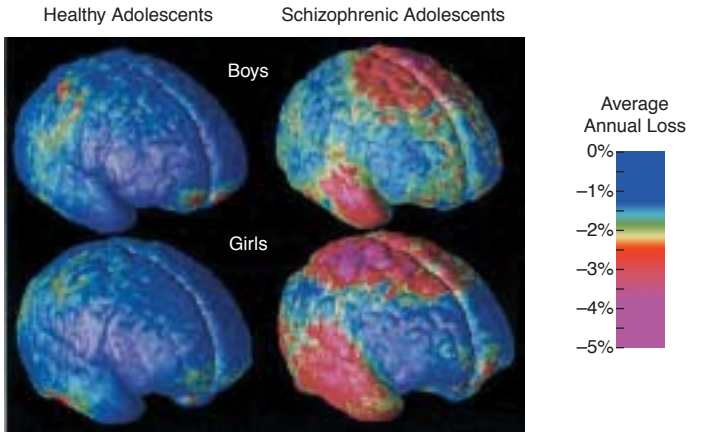
Figure 1. Stages of Illness in Schizophrenia[a]



[a]Based on Lieberman et al.[2]

Figure 2. Rate of Gray Matter Loss in Schizophrenia[a]



[a]Reprinted with permission from Thompson et al.[3] The color scale indicates the percent of gray matter change that occurred annually over a 5-year period.

patients will have psychotic relapses. These relapses can occur because the patients do not take their medication on a sustained basis after they have recovered from the first episode of illness or because the treatment was not sufficiently effective. Whatever the cause, the majority of people with schizophrenia have more than one psychotic episode, and as they experience these recurrences, they usually do not respond as well or recover to the same level as they had during their initial episode. That is not to say that these patients do not respond to treatment—in fact, they usually do much better with medication than without—but their symptoms do not completely resolve, and they do not recover their premorbid level of functioning. This phenomenon of clinical deterioration does not occur in a clearly predictable, linear, stepwise fashion, but occurs over the course of repeated episodes. This clinical deterioration was the basis for Kraepelin's initial distinction between dementia praecox and manic depressive illness.

This pattern of clinical deterioration is characteristic of progressive brain disorders, usually called neurodegenerative disorders. It is seen in Alzheimer's disease, Huntington's disease, and Parkinson's disease, but in those cases, the disorder progresses to the point where the person dies or is so severely disabled that he or she cannot function at all. In schizophrenia, that is not the case. After a period of progression, the illness appears to reach a plateau during which people are residually symptomatic and functionally impaired but whose symptoms do not worsen beyond what occurs in the course of normal aging. This is considered to be the end stage of illness. People can remain in this chronic/residual state for many years as they age.

The Role of Brain Imaging

Dr. Lieberman related that debate has gone on for years as to whether schizophrenia is a neurodevelopmental or neurodegenerative illness. With the advent of brain imaging, researchers had a new way to investigate how the brains of patients with schizophrenia were changing over time in relation to the clinical course of the illness.

Thompson et al.[3] represented in graphic form the rate of gray matter volume loss that occurs in people with early-onset schizophrenia compared with that of a healthy control group (Figure 2). The color scale in the figure indicates the percent of gray matter volume change that occurred annually over the 5-year period that these individuals underwent magnetic resonance imaging (MRI) scans. The mean age of the participants in the study was 14 years. Age-dependent change in gray matter volume does not usually occur until after age 40 years. All of the brains in the adolescent control group are blue, indicating that there has been no change over the period of time that they have been followed. But in the schizophrenic patients, a patchy coloration indicates varying degrees of gray matter loss, ranging from 1% to as high as 4% per year, occurring in the temporal lobe, in the parietal lobe, and in the frontal lobes. These results show that, over time, these adolescents with schizophrenia have experienced a loss of gray matter, which, according to Dr. Lieberman, may reflect the underlying progressive process that drives the deteriorating aspect of schizophrenia.

Conclusion

According to Dr. Lieberman, the targets of treatment include not just symptom stabilization and remission but also prevention of deterioration. If patients are treated in their first episode of illness, then the physician is able to not just alleviate mental symptoms and disturbances but also to prevent the progression and further clinical deterioration from occurring. Dr. Lieberman stated that he believes that antipsychotic treatment, in general, can attenuate this process, and that specific atypical antipsychotic drugs in particular may be able to prevent this progression.

It is easier, given the current pharmacologic and therapeutic tools that are available, to prevent the damage that schizophrenia causes in patients' brains than it is to restore function after damage has occurred. Physicians can prevent the progression of illness and the deterioration that it causes by using pharmacotherapy in a timely and sustained fashion, but if the chance to prevent that deterioration is missed, then the ability of the current treatments to restore the patient is decreased.

Schizophrenia: A Neurodevelopmental or a Neurodegenerative Disorder?

Dolores Malaspina, M.D., M.S.P.H., began her presentation by stating that, despite the advances that have been made in identifying important risk factors for schizophrenia (including susceptibility genes, prenatal exposure to stress or infection, and advanced paternal age), physicians still cannot prevent or cure the disorder, which remains a large part of the psychiatric illness burden. She reiterated Dr. Lieberman's point that within the first few years after the onset of schizophrenia, many patients undergo a clinical deterioration that leads to occupational and social disabilities. Preventing this early deterioration may markedly improve the long-term course of schizophrenia.

It was based on observing this deteriorating course in early adulthood—after an apparently normal childhood—that Kraepelin first theorized that the key pathophysiology of schizophrenia was one of neurodegeneration. Dr. Malaspina explained that, although the current consensus favors a neurodevelopmental model for the origins of schizophrenia, strong evidence exists for both hypotheses, and abnormal neurodevelopment and later neurodegeneration are not exclusive processes. They may predominate at different illness stages and in different subtypes of the disorder. It is possible that the onset of a neurodegeneration pathology shortly before the onset of the illness determines who among those at risk will develop psychosis and who among those with psychosis will develop deterioration.

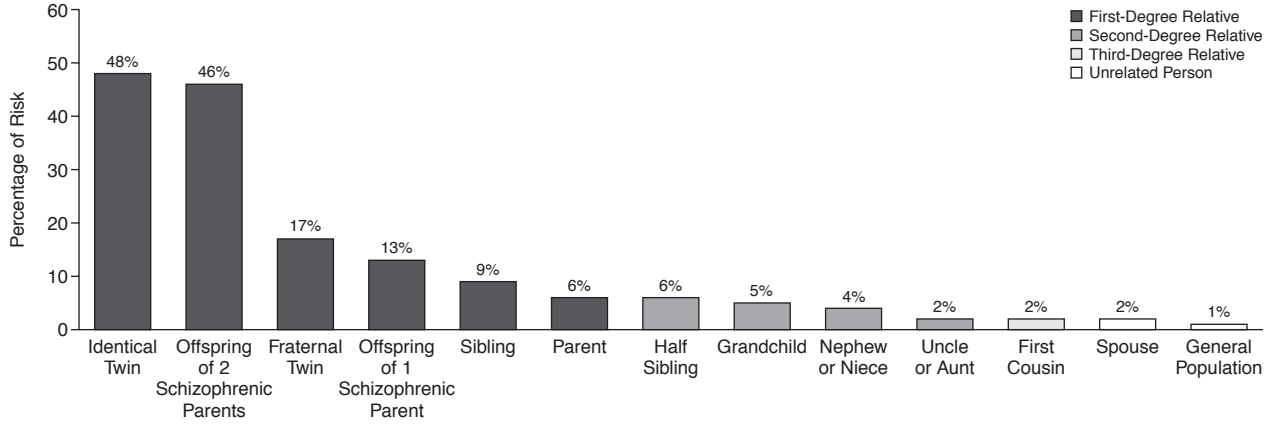
The Neurodevelopmental Hypothesis

Dr. Malaspina noted that from early life onward, many individuals who will later develop schizophrenia have subtle, nonspecific abnormalities that indicate pathology during brain development. These findings include deficits in verbal memory, gross motor skills, and global attention, along with social withdrawal, and, in some cases, a lower intelligence. Many who go on to develop schizophrenia also have minor physical anomalies, particularly finger, toe, and craniofacial abnormalities such as a high, arched palate. The origins of the developmental abnormalities are thought to be genes and/or harmful prenatal exposures.[4]

One of the best clues to the etiology of schizophrenia came from Kraepelin, who observed that relatives of patients often had a few signs of the disorder themselves. There is a rapid decrease in risk as relationship to the patient gets more distant (Figure 3).[5] However, the same identical twin data that is used to show that schizophrenia has a strong genetic component also shows that genes do not explain all of the risk for developing schizophrenia, because an identical twin with the same genetic makeup as an individual with schizophrenia has only a 48% chance of developing the disease. Additional exposures or events may determine risk and illness course.[6]

Humans and other mammals do not simply develop in the womb from a blueprint of their DNA, but in fact, the fetus is in constant interaction with maternal circulation. That maternal environment provides the fetus with information about which genes should be turned on and which should be silenced. Some of that information

Figure 3. Degree of Risk for Schizophrenia[a]



[a]Data from Gottesman and Shields.[5]

affects the lifetime expression of genes, providing genetic code separate from DNA that determines which genes will be expressed. Only 20% of a gene is expressed in any given cell,[7] which means that additional information is needed to determine which genes are expressed and which genes are silenced. This information is the epigenetic code, and it serves to control gene expression throughout the lifetime. Some of the environmental response that is seen is actually related to these epigenetic changes that alter gene expression. Data showing that the father's advanced age is a risk factor for schizophrenia suggest that paternal inheritance may influence how genes are turned on or off.[8]

Nongenetic factors, including environmental and early exposures, also play a role in the development of the disease. These factors include intrauterine exposures, such as maternal medical conditions, pregnancy complications, and prenatal stress and infection. For example, a fetal exposure to malnutrition in the womb can lead to a higher risk for obesity as an adult, and a fetus exposed to severe maternal stress will develop a greater stress sensitivity. Other factors include exposures that occur later in life such as cannabis use, which may triple the risk for schizophrenia[9]; severe stress, which in those with stress sensitivity may double the risk[10]; and traumatic brain injury, which may triple the risk for an individual compared to family members.[11]

The Neurodegeneration Hypothesis

According to Dr. Malaspina, despite the strong support for developmental origins, increasing evidence suggests that a degeneration of neuronal functioning occurs soon after the onset of psychosis. This degeneration can be seen in the declining function and cognitive ability and intelligence test scores of patients with schizophrenia and is also evident in postmortem neuroimaging data.

In this hypothesis, Dr. Malaspina explained, the neural abnormality that leads to psychosis remains latent. It arises as the individual's brain develops and stays hidden until either normal processes cause the maturation of the brain or an unknown second assault unmasks it. The second assault could be an event around or before the time of psychosis that leads to changes in the brain function that trigger the psychosis and the deterioration. If it is true that the abnormality that leads to psychosis remains latent, then there is a possibility that early adequate treatment may offer neuroprotection. The clinical symptom of psychosis may be a marker of an underlying pathophysiology that leads to neural damage.

Treatment Implications

Dr. Malaspina emphasized that clinical interventions that prevent deterioration deserve great attention. It is important for physicians to treat patients early in the course of their disorder—preferably, as soon as their symptoms begin. In a study by Harkavy-Friedman et al.,[12] adult patients with schizophrenia were separated into 2 groups according to whether they showed deterioration with loss of function between episodes or if they showed a functional recovery between episodes. When the data were analyzed, the patients who showed deterioration had a greater number of symptoms before their schizophrenia was identified and treated than those who showed a good interepisode recovery. In those individuals, there had been less psychopathology before the presentation of psychosis.

Effective treatment is also crucial. The goal of treatment should be the full remission of psychotic symptoms. Many families and treatment settings tolerate a simple decrease in psychotic symptoms, but this may not be the best medical care for patients. Tolerance of psychotic symptoms, if they are connected to an underlying neurodegeneration, could be problematic for patients in the future.

Furthermore, physicians should also treat patients extensively. Medication alone is sometimes not sufficient in

treating psychotic symptoms, and patients can benefit from adjunctive cognitive, behavioral, and other therapies. These therapies can decrease patients' arousal and suspiciousness, help them process information, reduce psychotic symptoms, and optimize psychosocial outcome. Helping patients continue to function well early in their course of illness can lessen the decline in their functional capacities. Some treatment centers use job coaching, cognitive remediation, and other strategies to achieve and retain a full functional recovery. All of these efforts are aimed at improving the quality of life for individuals with psychotic conditions, which can decrease the stigma of chronic psychiatric disorders.

Conclusion

Dr. Malaspina reiterated that clinicians should move forward in their understanding of schizophrenia to do everything possible to limit patients' psychotic symptoms and provide interventions that might curtail underlying neuropathology and neurodegeneration. The morbidity of schizophrenia may be greatly reduced by earlier and more effective treatments.

Although efforts are underway to prevent the onset of psychosis in prodromal cases, comparable research and clinical efforts are needed to try to curtail clinical deterioration in those patients who have already experienced psychosis and the condition of schizophrenia. In these patients, the clinician should adequately treat the psychotic symptoms that are present to aid in preventing future deterioration.

Neuroprotection in Schizophrenia

L. Fredrik Jarskog, M.D., began by stating that emerging evidence suggests that the loss of functioning in schizophrenia is not a static phenomenon but rather a progressive process following the onset of psychosis. Therefore, one of the key questions for physicians who treat patients with schizophrenia is whether treatments are available that can provide meaningful neuroprotection and slow the progressive loss of function.

A practical definition of neuroprotection is an intervention that helps to maintain the functional integrity of the brain in response to neurobiological stress, explained Dr. Jarskog. Given the evidence for progressive deterioration in schizophrenia, this definition suggests that psychosis is associated with some form of neurobiological stress that could benefit from neuroprotection. This protection could be in response to either actual loss of function (therapeutic interventions) or anticipated loss of function (prophylactic interventions).

Evidence for Neurodegeneration in Schizophrenia From Brain Imaging Studies

Dr. Jarskog related a study by Pantelis et al.[13] in which the researchers recruited patients who were not yet psychotic but who were at high risk for becoming so—patients with attenuated psychotic symptoms, a family history of psychosis, and the onset of functional decline. Patients received an MRI scan at baseline and then again after 12 months or at the onset of psychosis, and the results were analyzed to determine if there was any loss of gray matter. Only those patients who later converted to psychosis demonstrated progressive gray matter loss in the cortex. This loss was particularly seen in the orbito-frontal areas, in the medial and the inferior temporal lobe, in the cingulate gyri, and in the cerebellar cortex. These data suggest that even during the very early stages of clinical manifestation—i.e., during the prodromal period and conversion to psychosis—schizophrenia is associated with neurostructural changes that parallel the functional decline.

Dr. Jarskog also discussed the Thompson et al.[3] study showing excess cortical gray matter loss in prefrontal, parietal, and temporal lobes when compared to normal adolescents that Dr. Lieberman discussed in his presentation (see Figure 2). In addition, there was a gender-specific finding, in that boys tended to have more loss in the prefrontal areas, whereas girls tended to have more loss in the parietal and superior temporal lobes. This gender finding suggests a potentially more aggressive neuroprogressive course in males and further demonstrates the existences of neurostructural correlates to the functional decline that is seen in schizophrenia.

Potential Underlying Mechanisms of Neurodegeneration

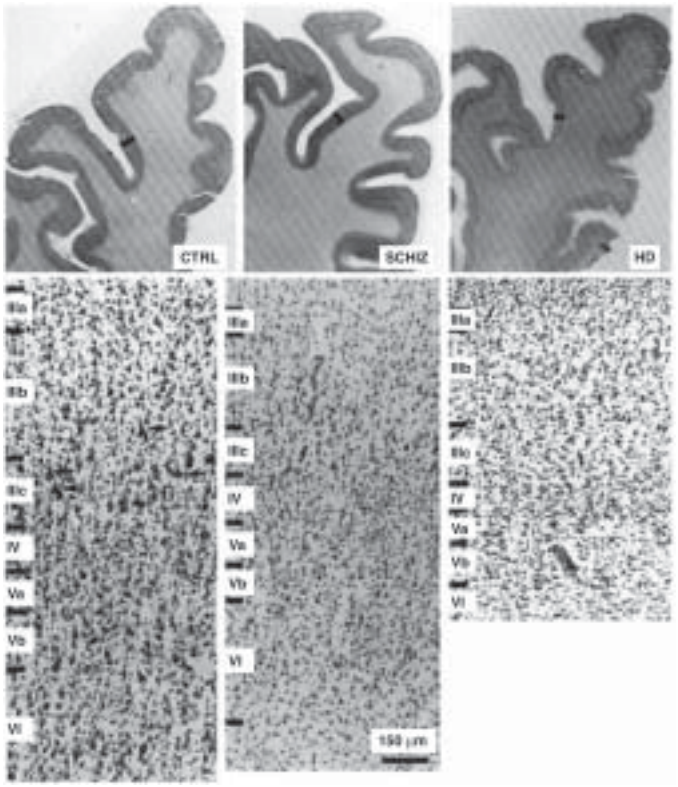
Dr. Jarskog went on to discuss potential underlying mechanisms that could contribute to this loss of gray matter in patients with psychosis. One leading hypothesis for gray matter loss is glutamate excitotoxicity.[14] Phencyclidine (the recreational street drug PCP) and other glutamate antagonists can mimic multiple dimensions of schizophrenia in otherwise healthy individuals. The hypothesis is that hypofunction of the *N*-methyl-D-aspartate receptor on inhibitory neurons of the GABAergic subtype can in turn disinhibit excitatory glutamatergic neurons, which then results in excess glutamate release and excitotoxicity. This theory has been difficult to support with evidence in postmortem brain tissue, possibly because it occurs on a much more limited scale and only during discrete intervals as compared to widespread excitotoxicity seen in certain classic neurodegenerative disorders.

Altered apoptosis is another mechanism that has been proposed to contribute to the loss of gray matter in patients with psychosis. Dr. Jarskog

said that he and his colleagues[15,16] have examined regulatory proteins of apoptosis (e.g., Bcl-2, Bax) in postmortem brain tissue and found evidence that vulnerability to apoptotic activation may be increased in schizophrenia. However, there is no evidence of active cell death in the postmortem cortex of patients with chronic schizophrenia, suggesting that, if excess apoptosis occurs, it is at an earlier stage of illness.

Other mechanisms that have been considered as possible mechanisms contributing to the loss of gray matter in patients with psychosis include oxidative stress, mitochondrial dysfunction, and reduced neurotrophic support, but more evidence is needed in this area.

Figure 4. Photographs of Sections From the Prefrontal Cortex of Healthy Control Subjects and Individuals With Schizophrenia or Huntington's Disease[a]



[a]Reprinted with permission from Rajkowska et al.[17]
Abbreviations: CTRL = healthy control subjects, SCHIZ = individuals with schizophrenia, HD = individuals with Huntington's disease.

Postmortem Evidence for Limited Neurodegeneration

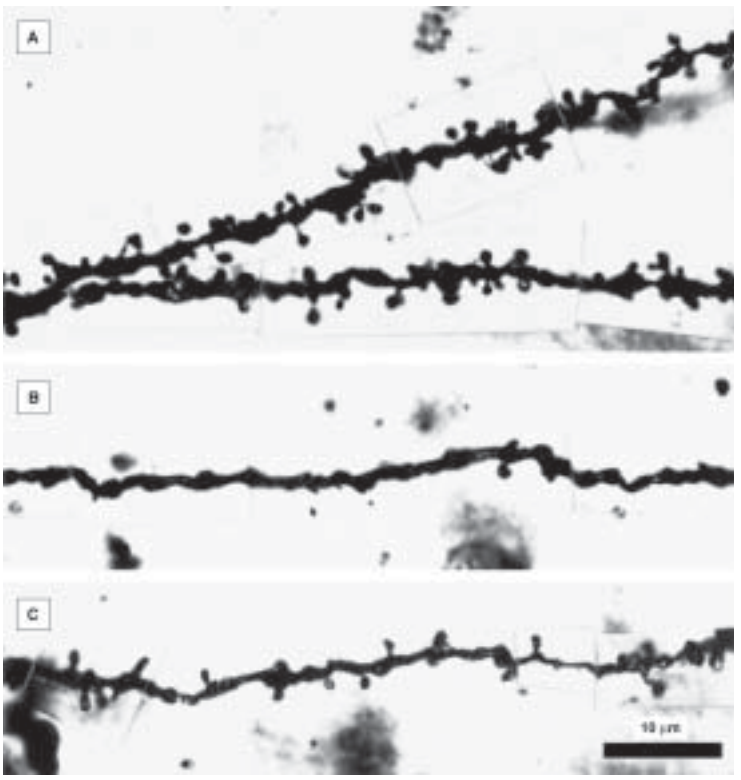
Dr. Jarskog then reviewed postmortem evidence for neurodegeneration in schizophrenia. Because postmortem analysis can only give a single snapshot of pathology at the end of life, it cannot differentiate whether observed changes occurred early in development or later in life, and if later in life, at what point—whether around the onset of psychosis or much later. Nevertheless, postmortem analysis provides information about whether there is a cellular basis for schizophrenia and whether it is consistent with the loss of gray matter seen in neuroimaging studies.

Rajkowska et al.[17] analyzed postmortem samples of the prefrontal cortex of individuals with schizophrenia and Huntington's disease as well as controls. Although the samples from individuals with Huntington's disease showed more tissue loss, a significant loss of gray matter was observed in the tissue samples from individuals with schizophrenia as well (Figure 4). Mild atrophy of the neurons that were present and a notable absence of gliosis in the tissue samples from patients with schizophrenia were also reported. The absence of gliosis is important because tissue samples from patients with classic neurodegenerative disorders typically display much gliosis, and in fact, that was seen in the samples from Huntington's disease patients. In the Huntington's disease patients' samples, atrophy of the neurons, loss of neurons, loss of gray matter or neuropil, and an increase of glial cells were all present. Dr. Jarskog explained that this study suggests that schizophrenia has certain aspects of neurodegeneration, but it must be of a more limited type as compared with classic neurodegeneration as evidenced by Huntington's disease.

Dr. Jarskog then reported that Glantz and Lewis[18] analyzed tissue specimens from brains of normal individuals and schizophrenia patients and found a reduction in the number of dendritic spines in layer 3 pyramidal neurons in the prefrontal cortex of patients with schizophrenia. In Figure 5, the top panel, A, shows dendritic spines, which are protrusions from the dendrites, in a normal individual, and the lower two panels, B and C, show dendritic spines in individuals with schizophrenia. Normally, each dendritic spine has 1 synapse, so fewer spines suggests that there are fewer synapses. Therefore, this study suggests that synaptic content is reduced in prefrontal cortical gray matter in schizophrenia and provides a cytoarchitectural basis for the study by Rajkowska et al.[17] showing reduced gray matter.

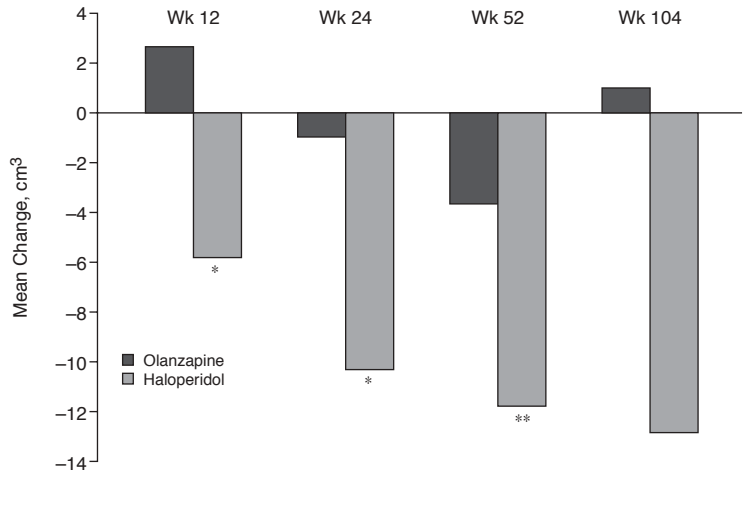
It can be asked, then, what is the potential for protecting against this neurostructural loss, and is it possible to alter the associated downward trajectory of functional decline following the onset of psychosis?

Figure 5. Micrographs of Tissue Specimens From Healthy Individuals and Patients With Schizophrenia[a]



[a]Reprinted with permission from Glantz and Lewis.[18] Panel A shows dendritic spines in a normal individual. Panels B and C show dendritic spines in individuals with schizophrenia.

Figure 6. Mean Change in Whole Brain Gray Matter Volumes From Baseline After Antipsychotic Treatment[a]



[a]Adapted with permission from Lieberman et al.[19]
*p = .002 vs. olanzapine.
**p = .049 vs. olanzapine.

Treatment Choice and Rate of Neurodegeneration in Schizophrenia

According to Dr. Jarskog, it may be possible to alter the progressive neurostructural changes following the first episode of psychosis by treating the patient with an atypical antipsychotic. Lieberman and colleagues[19] conducted a major study in which patients in their first episode of schizophrenia were randomly assigned to be given a typical antipsychotic, haloperidol, at 2 to 20 mg/day, or an atypical antipsychotic, olanzapine, at 5 to 20 mg/day, for 2 years. MRI assessments were performed at baseline and at weeks 12, 24, 52, and 104.

Beginning at week 12 and continuing through week 52, the patients given the typical antipsychotic showed significantly ($p = .002$) more loss in whole brain gray matter volume than the patients treated with the atypical antipsychotic (Figure 6). The trend continued to week 104 but most likely lost significance due to patient attrition. The same pattern of loss was seen in specific cortical subregions. For example, the patients treated with haloperidol showed significantly ($p \leq .003$) more loss of frontal cortical gray matter volume during weeks 12 and 24 than the patients treated with olanzapine. In the temporal cortex, the pattern was somewhat different but quite provocative. In the haloperidol-treated patients, there was no significant change in the temporal cortical gray matter volume, but in the olanzapine-treated patients, a small but significant increase in temporal cortical gray matter emerged, suggesting not only neuroprotection, but also a possible neurotrophic effect.

Importantly, neurocognitive assessments in this study indicated that, for haloperidol-treated patients, less improvement in neurocognitive function was associated with greater loss in cortical gray matter, including whole brain, frontal cortex, and parietal cortex. Since the level of neurocognitive function has been identified as the strongest predictor of functional outcome in schizophrenia,[20] these data

suggest that, in comparison to haloperidol, olanzapine offers functional advantages that derive from neuroprotective properties at the neurostructural level.

There are several possible theories that could account for the observed MRI effects. One is that haloperidol has a direct neurotoxic effect on gray matter that olanzapine does not have. Another theory is that the underlying pathophysiology of schizophrenia is associated with a loss of cortical gray matter, and olanzapine has a protective effect against this loss that haloperidol does not have. Unfortunately, to distinguish between these two possibilities would have required a placebo control group, which was not an option ethically. Currently, researchers are relying on animal studies and other preclinical studies to try to distinguish between these theories.

Conclusion

Dr. Jarskog concluded that, while schizophrenia is a neurodevelopmental disorder, it also seems to encompass limited neurodegenerative features. Strategies aimed at reducing gray matter loss hold promise for improving functional dimensions of the illness. The fact that gray matter loss may be decreased with an atypical antipsychotic suggests that these agents may offer a degree of neuroprotection that is not provided by typical antipsychotics. While the underlying mechanisms of the disorder remain uncertain, evidence of improved outcomes suggests that neuroprotection in schizophrenia is possible.

Drug names: haloperidol (Haldol and others), olanzapine (Zyprexa).

Disclosure of off-label usage: The chair has determined that, to the best of his knowledge, no investigational information about pharmaceutical agents that is outside U.S. Food and Drug Administration–approved labeling has been presented in this activity.

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