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Understanding Schizophrenia

TO THE EDITOR: The studies aimed at helping us to understand schizophrenia, reviewed by Robert Freedman, M.D. (1) in the March 2007 issue of the *Journal,* are intriguing. But doesn't much of the work still seem to focus on one or a few features, while missing the essence? For example, do studies focusing on positive symptoms help to explain negative symptoms, which seem integral to schizophrenia and which severely limit functioning? Testable hypotheses are good, but do we know enough about the complex brain mechanisms that are malfunctioning in schizophrenia to attempt to study or explain them? Possibly not.

For example, schizophrenia is a uniquely human illness (despite useful animal models). A unique aspect of human mental function is our ability to form an internal mental image of the world, replete with images, memories, thoughts, and emotions, to manipulate it, and to imagine how different actions on our part might lead to different goals or results. This ability has led to much of the advancement of civilization. The human brain operates on two levels at the same time: one in contact with reality, the other focused on internally generated "mental images" (when dreaming, internal images are "unopposed"). Whether this "dual processing" is related to the lateralization of the brain (i.e., two brains working somewhat independently) or to the enlargement of the frontal lobes (both relatively unique features of the human brain) or both is unclear.

In schizophrenia, the relationships between internally derived perceptions and outside reality are out of balance; internally derived perceptions are excessively strong (and seem to be external). This conceptualization can explain both positive and negative symptoms. Positive symptoms are because of internally derived perceptions being stronger than usual. Negative symptoms are more attributable to the "weakness" of focus on external reality. Schizophrenia patients are less concerned with how they look, smell, and interact with others, with accomplishments in the real world, and with whether others understand them. They are more concerned with internally derived perceptions.

If the complex mechanism that creates mental images malfunctions, can one measure it? Is the size of the frontal lobe, or blood flow, or levels of dopamine, or an evoked potential, going to tell us much about the relative strength of the mental images? Probably not, since the creation and manipulation of mental images probably involve much of the brain and innumerable neurotransmitters, receptors, and connections. It may be that our complex technologies, although impressive, are still unlikely to clarify the malfunction that causes schizophrenia.

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Restarting Clozapine Treatment During Ablation Chemotherapy and Stem Cell Transplant for Hodgkin's Lymphoma

TO THE EDITOR: We describe an unprecedented case of a patient with bipolar mania who was successfully restarted on clozapine treatment while receiving ablation chemotherapy and an autologous stem cell transplant for Hodgkin's lymphoma. While a few cases of clozapine use with cancer chemotherapy have been documented (1–4), our case is unique in that a stem cell transplant was involved.

"Mr. S" was a 39-year-old white male with a history of bipolar I disorder who presented on a responsive regimen of clozapine (300 mg b.i.d.) and lithium (1800 mg every night), with the occasional addition of benzodiazepines, for 10 years. In February 2006, he was admitted with an exacerbation of his mania, characterized by pressured speech, expansive affect, decreased sleep, and psychomotor agitation. He reported weight loss with episodes of night sweats, pruritic rash, and painless lymph node swelling. Oncology diagnosed the patient with Hodgkin's lymphoma, nodular sclerosing type. Clozapine was discontinued because of the concern of clozapine-induced agranulocytosis, and the patient was switched to a regimen of olanzapine (30 mg b.i.d.). Lithium and lorazepam were continued.

Subsequently, in July 2006 the patient presented with a decompensation of his bipolar disease, despite treatment with olanzapine. Because of his poor response to olanzapine, we considered restarting clozapine, even in the context of active Hodgkin's lymphoma.

The patient was scheduled to receive ablation chemotherapy and a stem cell transplant during that hospitalization. Concerned about the possibility of leukopenia from Hodgkin's disease treatment, we contacted IVAX pharmaceuticals to determine whether the patient would be eligible for a waiver, because generally clozapine must be immediately discontinued if a patient develops leukopenia (white blood cell count <3000 cell/mm^3 with a satisfactory neutrophil count) or neutropenia (neutrophil count <1500 cell/mm^3). It was decided that the benefits outweighed the risks. The waiver was granted and clozapine was restarted.

In August 2006 the patient was transferred to another hospital to receive his stem cell transplant. During that treatment, his white blood cell count was 0.1 cell/mm^3

with ANC <0.02. Postprocedure, his white blood cell count was 9.9 cell/mm^3. He returned to our inpatient unit in September 2006. His white blood cell count since then has remained between 5.5 and 9.9 cell/mm^3.

To our knowledge, this is the first reported case of successful use of clozapine during life-saving ablation chemotherapy and a stem cell transplant. Clozapine should be used with caution due to the risk of leukopenia and the varying degrees in which it affects patients. However, this suggests that in some cases after other options have been exhausted, it is worthwhile to consider restarting patients on clozapine to control acute mania while undergoing stem cell transplant.

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Initiation of Methamphetamine Abuse During Interferon Treatment

TO THE EDITOR: Interferon therapy for chronic infection with hepatitis B or hepatitis C virus produces clinical depression in up to one-half of patients treated. Adverse effects of interferon increase the risk of relapse to opiate and cocaine use during therapy in former injection drug users, which may in turn reduce the likelihood of achieving a sustained virologic response (1–3). To reduce the risk of relapse, interferon therapeutic guidelines stress the importance of pretreatment assessment of all patients for anxiety, depression, and substance abuse disorders (4). We report the case of an additional and previously undocumented risk during interferon treatment: initiation of crystal methamphetamine abuse.

"Mr. B," a 48-year-old hepatitis C virus-infected study participant with previously diagnosed depression, started interferon therapy in June 2003. He completed a full course of interferon and experienced a sustained virologic response. He reported using methamphetamine for the first time while receiving interferon: "My hep[atitis] C got worse and I started on the interferon program. I already suffered from depression and that just nailed me with depression. On a business trip to the city, a gay friend offered crystal…and that gave me the high that I needed. That just got me out of my depression, got me out of feeling sick from the interferon, made me feel good."

Within weeks, Mr. B progressed to daily problematic use of methamphetamine. Although previous human immunodeficiency virus (HIV) serologic test results were reportedly negative, his first result following initial use of methamphetamine was reactive.

The increased risk of relapse to substance abuse during interferon therapy is widely appreciated. Our case alerts clinicians to the initiation and progressive use of methamphetamine during interferon therapy, a previously undocumented risk. Patients experiencing interferon-induced depression may find the acute methamphetamine-induced increases in monoamines (principally dopamine) alluring (5).

In the United States, Canada, and Australia, the prevalence of occasional methamphetamine use among men who have sex with men ranges between 6%–40%, at least 10-fold higher than the rest of the population; the prevalence of methamphetamine use is even higher among men who have sex with men with HIV infection or a history of substance abuse (6).

When administering interferon therapy to men who have sex with men and members of similarly vulnerable communities with a high prevalence of methamphetamine use, clinicians should counsel patients about methamphetamine use and routinely evaluate them for pretreatment antidepressant therapy.

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