Treating schizophrenia

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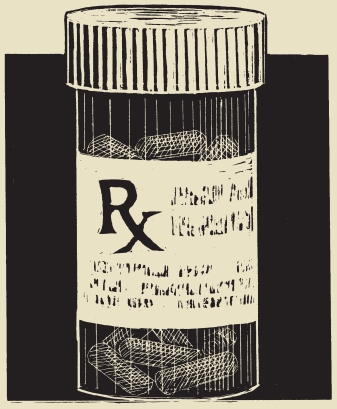

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Considerable research is focused on helping people who suffer from schizophrenia—a devastating psychiatric disease that affects one percent of the population in the world and over two million people in the United States. This chronic, severe, and disabling disorder is characterized by what psychiatrists call "positive"—or psychotic—symptoms, such as hallucinations and delusions, as well as by "negative" symptoms, such as lack of motivation and difficulty interacting with other people. Schizophrenia's onset is typically in late adolescence or early adulthood, and it produces a significant disability in most people who have it.

For more than 50 years, antipsychotic drugs have been used to treat schizophrenia. Traditional antipsychotic medications, like haloperidol and chlorpromazine, block the action of dopamine, one of the chemical neurotransmitters in the brain. These medications control hallucinations and delusions and may allow patients to live outside of a hospital, but they cannot cure the disease and they do little to reduce the negative symptoms. Therefore, even people who are under treatment often continue to live isolated and lonely lives.

Speculation: Psychiatrists have long speculated about the causes of schizophrenia. In the 1950s, many experts believed that family influences and irregular parenting were key factors. By the 1960s, however, scientists began to understand that schizophrenia was a biological disease and that its cause was at least partially genetic. Researchers in Scandinavia determined that genetics played a role when they found that schizophrenia was more likely to occur in both members of identical twin pairs than of fraternal twin pairs, even when different adoptive families raised the siblings.

Scientists have also long suspected that the brain's structure is different in people with schizophrenia but had no proof of this until the mid-1970s, when computerized tomography scans came along. This x-ray procedure, which can produce cross-sectional images of brain tissue, confirmed that there are structural abnormalities in the brains of those with schizophrenia. Recently, researchers at Dartmouth and elsewhere have begun using functional magnetic resonance imaging (fMRI) to assess differences in the way the brains of those with and without the disease work. By showing changes in blood oxygen levels during brain activity, fMRI scans provide useful information about how the brain functions when a person performs specific tasks. Dartmouth researchers are now using fMRI to study the brain reward circuit—a network of brain cells involved in experiencing pleasure or meaning in everyday life—in an attempt to understand the high rate of substance abuse in patients with schizophrenia.

In the 1980s, scientists developed animal models to explore a neurodevelopmental theory of schizophrenia. Studies showed that, in young rats, injury to the brain's temporal lobe led to problems in the prefrontal cortex, an area that is abnormal in people with the disease.

This shed light on how schizophrenia could be silent in childhood and adolescence, with symptoms appearing in late adolescence or early adulthood. Thus a brain abnormality may be present in a fetus or child but not trigger psychotic symptoms until the brain matures. This neurodevelopmental theory means there may be a way either to slow down the natural progression of schizophrenia or perhaps even to prevent it from developing altogether. Studies are under way at Dartmouth and elsewhere to determine whether early intervention strategies can help.

Drugs: The 1990s saw a breakthrough in pharmacological treatment. Traditional antipsychotic drugs were only modestly effective in treating schizophrenia's symptoms, so scientists designed new drugs and tested chemical relatives of older drugs. Clozapine, chemically related to an older drug, loxapine, turned out to be more effective than loxapine or other medications used to treat schizophrenia. Clozapine blocks receptors for several neurotransmitters—dopamine, serotonin, and norepinephrine—and it decreases both positive and negative symptoms. Patients on clozapine relapse less often and exhibit less alcohol and substance abuse, the most common co-occurring disorder in people with schizophrenia. Dartmouth researchers are trying to find the keys to clozapine's success and are exploring whether the drug improves the functioning of the brain-reward circuitry that is thought to be deficient in schizophrenia. The availability of this broad-spectrum medication has unleashed a new era in treatment development.

Effects: Although clozapine appears to ameliorate some neurodevelopmental abnormalities in people with schizophrenia, it has serious side effects—such as lowering white-blood-cell counts in some people—that limit its widespread use. Nevertheless, scientists hope that clozapine, or a safer, newly developed version of the drug, may be effective if given to patients early in the course of the disease.

These breakthroughs in neuroimaging, animal-model studies, and pharmacology, combined with other advances—such as the development of gene profiles to determine who is predisposed to schizophrenia and who may respond to particular treatments—hold great promise. For example, Dartmouth scientists are searching for biomarkers of optimal treatment and hope to target a particular subtype of schizophrenia, treat it earlier, and maybe even prevent its onset. Perhaps the day will come when the malignant course of this devastating disorder will be nothing more than painful history. ■

The "Bench to Bedside" essay explores the research underlying advances in clinical medicine. Green is chair of psychiatry and the Raymond Sobel Professor of Psychiatry.