Mending the Mind

The early identification of young adults at high risk for schizophrenia is essential for their successful treatment. How can we find and help them? Psychiatrist and researcher Jeffrey Lieberman, who has devoted his career to understanding this illness, outlines new pathways to detection and recovery.

Illustrations by SANDRA DIONISI

WHEN BRANDON STAGLIN WAS FIRST HOSPITALIZED and told he had schizophrenia, a serious mental illness, he was outraged. Brandon was a student at Dartmouth and had ambitious plans. Now his parents were insisting that he take medications that produced unpleasant side effects. ¶Faced with a suddenly uncertain future, Brandon sank into depression. What pulled him out after that first psychotic episode were clozapine and chimpanzees. Brandon had gone back to the hospital for two weeks in the fall of 1990, and his medication had been switched to clozapine. Not long after, his mother heard him singing in his room. Over the next months, while seeing a psychiatrist and continuing to take his medication, Brandon audited classes at UC Berkeley and volunteered to work on a chimp study at the Oakland Zoo. He was still depressed, though, and at one point suicidal. But he felt conflicted: Did he really want to die? It occurred to him that he still hadn't seen a certain chimp at the zoo enact a dominance display. What a spectacle that would be to see firsthand! he thought. "And by extension, I thought of all the other experiences that were waiting for me in life," he reflects. "And so I decided it was worth living."

Within six months, Brandon was back at Dartmouth. He stayed on his medication and continued to see a psychiatrist. He was still struggling with strange thoughts and irrational fears, but he was determined, and in 1993 he graduated with honors. He got a job in Palo Alto, California, designing communications panels for satellites. It was the kind of work he'd long dreamed of doing.

Brandon began planning for a graduate degree and was accepted to programs at MIT and Stanford. There was one problem: He knew he'd never be able to keep up with his studies if he was sleeping nine hours a night—which clozapine caused him to do. Without consulting his doctor, he began to cut back on his medication. The hallucinations returned, now accompanied by obsessive-compulsive behaviors. He began acting erratically. He resigned from his job and wound up back in the hospital.

His second recovery was harder. He was living by himself in San Francisco, lacking the motivation to do anything. What helped to get him back on his feet was a clinical trial at the San Francisco VA Medical Center, which used cognitive training to strengthen neural pathways in the brain, specifically those circuits weakened or damaged by schizophrenia. Brandon practiced the training five days a week for ten weeks, playing computer games that required him to differentiate among various auditory tones. He began to regain his conversational skills and his ability to respond appropriately to what others said. His desire to get on with his life returned.

Why Timing Is Key

Schizophrenia is a low-incidence but high-prevalence disease, meaning that relatively few people develop it each year (15.9 per 100,000 people) but once you do, you have it for life (the lifetime prevalence is 4.3 per 1,000). The illness isn't something you contract and get over. It is a condition that doesn't go away but that you can live with if you have the appropriate treatment.

Treating schizophrenia is complicated by its heterogeneity (as well as the existence of conditions that imitate it) and by the need to intervene early. The window for intervening and preventing the illness from progressing varies for each person but is limited roughly to the first two to five years of the disease, including the prodromal (presyndromal) stage. When that window has closed, it's not that there is no point in treating people—in fact, their need for services may increase—but the goals and expectations have to be adjusted. We shouldn't encourage patients to set goals that are too low, but we have to be realistic and work with them to achieve a newly imagined and meaningful life.

Treatment of schizophrenia began with the discovery of chlorpromazine and the subsequent proliferation of antipsychotics, followed by the introduction of clozapine and incrementally improved second-generation antipsychotic drugs. Psychosocial treatments were developed, validated, and applied in parallel. But it was the disruptive insight of the importance of early detection and intervention that spurred the combining of these treat-

ments. Their application to early-stage patients has transformed care for this most malignant of mental maladies.

Finding High-Risk Individuals

Once we understood that the critical determinant of patients' outcome was prompt intervention with state-of-the-art treatments, it didn't take long to realize that a strategy of preventive intervention could be extended to patients in the prodromal stage of illness.

Our current approach is to identify people considered at clinical high risk (CHR) for developing a psychotic disorder. CHR is defined by a series of nonspecific symptoms and behavior changes known as attenuated positive symptoms, including:

- Exhibiting attenuated and not overt psychosis-like symptoms
- Being easily distressed—for example, by social interactions or the behavior of family members
- Becoming interested in a new religion or turning over a new philosophical leaf
- Becoming intolerant and complaining of things that are commonplace
- Withdrawing from old friends and hanging out with a new crowd or isolating oneself from social interactions
- Wanting to be more independent and not trusting or relying on family
- Having unusual beliefs or strange or suspicious thoughts but lacking conviction about them
- Experiencing cognitive complaints, such as feeling as if one's brain freezes up when spoken to or that the demands of daily life have become overwhelming

The idea of treating high-risk patients before the illness fully takes hold is not yet ready for prime time. Only about a third of people who meet the criteria for CHR eventually develop schizophrenia. This means that a person considered to be at clinically high risk can be confirmed as having been in the prodromal stage only after his or her symptoms have worsened and met the criteria for a diagnosis of schizophrenia.

Though the study of CHR in schizophrenia, and the methods for detecting and treating it in the prodromal stage, is still a work in progress, criteria have developed for identifying those at high risk. One is age of onset: People are generally considered CHR only if their attenuated positive symptoms develop between the ages of around 14 and 30. The other concerns the time course of symptoms. The prodrome is a dynamic period when symptoms develop and progress relatively quickly to schizophrenia. Therefore, only people with attenuated positive symptoms that are new or have worsened in the previous year can be considered clinically high risk.

Known Symptoms, Unknown Outcome

The CHR criteria can identify people at heightened risk for schizophrenia. The next challenge is to improve the capacity to predict who among this population will develop the illness. The 2015 North American Prodrome Longitudinal Study (NAPLS) revealed that very few of the symptoms manifested by CHR patients and measured at baseline predicted later outcome. The specific symptoms that best differentiated those who developed psychosis included unusual thought content and disorganized communication. Perceptual abnormalities, one of the most frequent symptoms at baseline, did not relate to later outcomes.

Other examples of high-risk symptoms include:

- Feeling as if things are unreal
- Ideas or preoccupations others find difficult to understand
- Changes in perception, such as hearing or seeing things others do not
- Feeling suspicious or mistrustful
- Withdrawing from friends and family
- Problems in school or at work
- Loss of interest or lack of motivation
- Changes in sleeping or eating patterns
- Decreased concern with appearance or clothes
- Confusion or trouble thinking clearly
- Changes in personality

If we are to extend early identification and intervention as a standard of care to the prodromal phase, two things must happen. First, criteria for a CHR diagnosis must improve so that the 70 percent false positive rate—individuals diagnosed with CHR who never develop schizophrenia—can be reduced markedly. This will require a validated diagnostic test, most likely using imaging, genetics, blood tests, or electrophysiological methods. Second, a treatment must be developed that is effective in alleviating prodromal symptoms and preventing the conversion to schizophrenia. While antipsychotic medications are very effective for syndromal schizophrenia, it is not clear if they are effective or warranted for attenuated symptoms in the prodromal stage. We don't want to treat people unnecessarily.

The prodromal period, when symptoms begin to develop and may progress, can make or break the course of the disease.

Numerous treatments, including antidepressants, benzodiazepine anxiolytics, lithium, and nutrients or food supplements used as therapeutic agents, such as omega-3, fish oil, and antioxidants, have been tried on CHR individuals. None has proven effective. Psychosocial treatments such as supportive

problem-oriented psychotherapy, cognitive behavioral therapy, and family therapy can be effective in alleviating symptoms by reducing stress and/or simply allowing time to pass so that the undefined condition can declare itself. This cautious watch-and-wait approach embodies the physicians' dictum *primum non nocere*: First, do no harm.

Crossing Into Psychosis

The incidence of CHR is estimated at about one in ten thousand. In order to connect with some of those people, CHR clinics do a lot of community outreach. They go to high schools and colleges and talk to teachers, students, and mental health counselors, educating them about warning signs: Maybe someone they know has stopped bathing or started saying strange things. They're acutely conscious of the fact that they are dealing with people at a critical moment. There is only one prodromal period, and it can make or break a person, not only in terms of disease progression but also in how they internalize stigma and relate to the illness.

Once someone comes to a CHR clinic, they are given a Structured Interview for Psychosis-Risk Syndromes, or SIPS, which assesses for three types of psychosis-risk syndromes. The key indicators for high-risk status are based on the scoring of positive symptoms (delusions, paranoia, grandiose ideas, hallucinations, and disorganized communication) according to their level of severity, frequency, degree of conviction, and behavioral impact.

Good clinicians also learn to recognize patterns and pick up on clues instinctively. What seems like nascent paranoia, for instance, may be a context-appropriate response to difficulties at home, at school, or in the neighborhood. A story that sounds highly unlikely or a sign of grandiose delusions may turn out to be true. Context is important as well. We have to avoid pathologizing "magical thinking" that aligns with someone's culture or faith. If the idea that you have a direct line to God is acceptable within your tradition, then perhaps it doesn't signal a problem; if a dialogue with God runs counter to your culture or faith, alarm bells ring. There is also the question of how a symptom is affecting someone's life. Are they talking to God and walking out into traffic or talking to God and becoming a humanitarian? Illness impairs, and implicit in the idea of a mental illness is that it harms the person who has it. In other words, we have to look at how the whole picture the person is presenting holds together—or doesn't.

The onset of schizophrenia seems to involve a very rapid multiplication or intensification of the indicators the SIPS picks up on, to the point where disparate symptoms begin to feed into one another in a way that, for the patient, makes sense. If someone is having a hallucinatory experience of hearing footsteps, it's easier for her to believe she's being followed. The delusion supports the hallucination, and what others might view as a breakdown, the person experiences as a breakthrough—a eureka moment when everything suddenly makes sense, and they have full conviction in their delusions and are most resistant to the idea that they are ill. Never mind that the pieces don't line up. The person will persist in trying to tie it all into a coherent narrative—an impulse common to all human beings—which can be like watching someone reason themselves into illness. One young man I knew described it to me as though he were "waking up to reality for the first time; like someone had yanked me out of *The Matrix*."

How We (Should) Treat Schizophrenia

There are five key elements of treatment that offer patients the best possibility of symptom relief, avoiding the illness's disabling effects, and achieving recovery: First, if you suspect symptoms, seek professional help as soon as possible. Second, antipsychotic medication is essential. It will be needed at the onset of illness and likely long after acute symptoms have subsided. Third, medication alone is not sufficient; psychosocial therapies and support services will also be necessary. Fourth, recovery requires a safe living arrangement, whether with family or friends or in a supervised residential facility. And fifth, every person affected by schizophrenia needs a reliable and caring family member, friend, or provider dedicated to supporting their recovery.

A number of things that helped Brandon recover are incorporated into the treatment model known as coordinated specialty care: He had high-quality medical care and medication management, supported employment, and the involvement of family. He also began treatment immediately after his first psychotic break. Early on, he had a psychiatrist he trusted and who persevered until they found the medication that worked best for him. Medication, Brandon feels, has been necessary but not sufficient for his recovery. Recovery isn't just about admitting you have a medical condition, he explains, or even being symptom free. It's about getting your life back, being able to do the things you care about. For recovery, he needed to reclaim agency. "The patient has to lead the definition of recovery," he says. "And

you have to be active and try to live again."

I look forward to discoveries that will improve clinical care, most likely in the form of diagnostic and prognostic biomarkers, and novel personalized treatments. A diagnostic test for mental illness is the holy grail, and much effort has gone into identifying biomarkers predictive of schizophrenia.

These technologies promise undreamed-of relief, but we shouldn't allow them to blind us to what we now can do to treat schizophrenia. In terms of medication, simply increasing the use of clozapine and long-acting injectables would significantly improve the quality of care and reduce the burden of illness on patients with schizophrenia. We know already that psychosocial treatments and coordinated specialty care work. What we don't know is how profoundly all of our lives—as patients, family members, citizens—could be changed for the better were these treatments to be properly funded and staffed. How long before we do the right thing? It's long past time.

What Is Recovery?

Over the previous half century, our attitude as a society toward the idea of recovery for people with schizophrenia has evolved from an impossibility to the point where a degree of recovery is regarded as achievable and even expected. The advent of the early-detection and intervention strategy has made substantial, even full, recovery a more realistic goal. Research on developing diagnostic measures and treatments for people in the premorbid or prodromal stage of schizophrenia offers the future possibility of prevention.

Studies examining middle-aged or older patients who had been ill for many years reported finding that most had improved. They were still symptomatic, but they managed their symptoms and were functional. Some studies noted that up to two-thirds of people diagnosed with schizophrenia experienced significant improvement over time, while many recovered completely.

I regard the interpretations of these studies as overly optimistic. Of the thousands of people with schizophrenia I have seen or treated, I have never known anyone to spontaneously recover completely and require no further treatment. Experience tells me that such instances are either extremely rare or nonexistent. What I have seen very often is the well-documented fluctuating and evolving course of the illness: Patients exhibit discrete florid psychotic episodes in the early stages, but as they get older and the illness progresses, their psychotic symptoms diminish in intensity and negative symptoms (anhedonia, or the inability to experience pleasure; lack of emotionality; poverty of thought) become more prominent.

The other source of evidence now cited for the possibility of recovery is the early-intervention psychosis research focusing on disease-modifying treatments. These studies I do view as confirming recovery, but the recovery-promoting effects, both biological and functional, of early-intervention strategies apply only to younger patients. The rest—the long-term ill—can benefit from treatments, but we don't have treatments that enable them to return to their pre-illness condition.

The episodic nature of severe mental illness enables significant recovery to occur even without complete symptom relief. Parallels can be seen with physical illnesses that might be episodic (rheumatoid arthritis, multiple sclerosis) but that don't prevent people from living full or meaningful lives. Yet a psychotic episode or a diagnosis of serious mental illness can shatter a person's sense of self in a way few physical illnesses do; in mental illness, the engine of recovery—the brain—is also the organ affected. One feels stigmatized. Lifelong goals seem suddenly out of reach.

It is essential to recognize how important connection to fellow human beings is for people with mental illness, as it is for everyone. People who are recovering talk about those who believed in them when they had no self-belief, who encouraged their recovery without trying to force it, and who tried to listen and understand when nothing was making sense. Brandon recalls how even when his family was very scared, they were always supportive. "There was a time I was really depressed," he says. "I remember walking into the dining room, and my father saying, 'There's a lot of love here, Brandon.' I couldn't feel love at that time, but hearing him say that inspired me to want to get better." Increasingly, peers play a part in this support. In order to serve as a role model, someone need not be fully recovered. In fact, the person who is only a few steps ahead can often be a more effective peer support than one whose achievements seem out of reach to the person on the receiving end.

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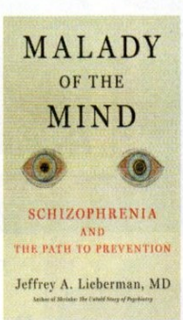
Clinicians, friends, and family can help a patient regain selfhood by recognizing which roles and activities still enable them to experience a sense of agency. Find out the person's pleasures and interests—the sense of meaning and purpose that has kept them alive. The notion of full citizenship is important to recovery—enabling participation for everyone in a context of rights, responsibilities, and a sense of belonging. ■



Jeffrey A. Lieberman, M.D., is a professor of psychiatry at Columbia University. He is the author of *Malady of the Mind: Schizophrenia and the Path to Prevention* and *Shrinks: The Untold Story of Psychiatry.*