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CURESZ FOUNDATION
Newsletter

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Comprehensive Understanding via Research and Education into SchiZophrenia

Treatment Resistant Depression (Part 2 of 2)

by **Stephen Rush**, *MD*

In the last article, we discussed what depression is and what treatments are typically used to treat depression. We also discussed Treatment Resistant Depression (TRD) and the challenges and burdens this illness presents for patients, clinicians, and communities. Depression that is treatment resistant, defined by the failure to respond to at least 2 trials of antidepressant medications, occurs in up to 30% of people. However, many patients classified as *"treatment resistant"* have had trials of multiple antidepressants and other medications, with limited positive effect on mood.

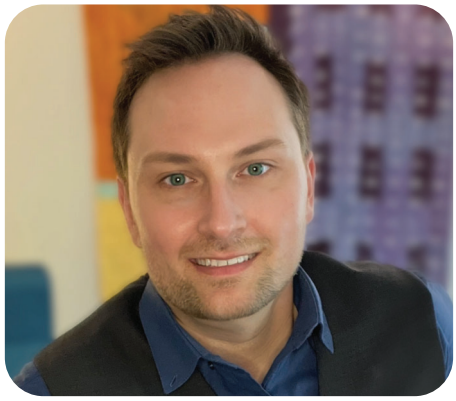
Hope for Recovery

There are several approaches to treatment of TRD when 2 or more antidepressant medications have not resulted in sufficient improvement.

One approach is the addition of a second medication that has been shown to increase response to an antidepressant, known as augmentation. FDA approved medications which can augment an antidepressant include Seroquel, Abilify, Vraylar and Rexulti, which are classified as *"antipsychotic"* medications though not used for that purpose here.[1,2,3,4]

In recent years there have been advances in treatments for depression including neuromodulation techniques such as Transcranial Magnetic Stimulation (TMS) as well as new medications such as esketamine. Another form of neuromodulation, electroconvulsive therapy, has been available for more than 50 years and has been demonstrated to be the most effective at treating depression, but is often avoided because of a history of pop-culture references that induce fear. The movie *"One Flew Over the Cuckoo's Nest"* is the most famous of these.[5]

Transcranial Magnetic Stimulation is a non-invasive treatment that uses magnetic fields to induce an electric current, targeted at specific brain regions thought to be underactive in depression. To achieve this, an electric pulse generator is connected to a magnetic coil placed over the brain region known as the dorsolateral prefrontal cortex. When electromagnetic pulses are applied to this area at a high frequency (10 times per second), the activity in the DLPFC increases and, subsequently, results in increased activity in other brain regions thought to be involved in depression. Treatment is done 5 days per week, Monday through Friday, for 30-36 total treatments (6-7 weeks) with each treatment lasting from 4 to 45 minutes. The effects of TMS on depression are typically not seen until sometime after 20 treatments are completed, at week 4. The antidepressant effect of TMS is associated with increased brain activity, increased dopamine and serotonin transmission, and increased production of Brain Derived Neurotrophic Factor (BDNF) which is a protein vital for maintaining the health of neurons and neural pathways.[6] Recently, there has been an increased focus on the role of BDNF in depression. Studies show an association between low BDNF levels and higher severity of depression and, in response to TMS, increased BDNF levels and neuroplasticity (the ability of the brain to form and reorganize neural connection).[7,8] TMS is not appropriate for people who have implanted or metallic devices such as aneurysm clips or coils and pacemakers. There are limited side effects that result from TMS treatment, including discomfort at the stimulation site and headaches. There is a known risk of seizures, though it is estimated that this side effect occurs in less than 1% of patients.[9]



Stephen Rush, *Professor of Clinical Psychiatry, University of Cincinnati*

Ketamine has long been used as an anesthetic agent that also has rapid-acting antidepressant effects. Ketamine can be administered through an IV, as an intramuscular injection and as an aerosolized nasal spray. Spravato, or esketamine, is a modified molecule derived from ketamine that was FDA approved for the treatment of treatment refractory depression and Major Depressive Disorder with acute suicidal ideation in 2019. This drug is self-administered by patients, under physician supervision, as a nasal spray. Both ketamine and Spravato are thought to have effects on at least 2 pathways in the brain: decreasing glutamate transmission at n-methyl-d-aspartate (NMDA) receptors and activating opioid receptors.[10] Dosing of this medication varies by patient and the antidepressant effect is usually seen within the first month, though may be dependent on continued dosing to sustain this response, done at frequencies that vary from weekly to monthly.[11] This treatment is generally well tolerated and side effects, including dissociation, alterations in heart rate and blood pressure, nausea, and sedation, typically resolve within 2 hours after administration.[12]

Electroconvulsive Therapy, or ECT, is a treatment where electricity is applied to the scalp with the intention of inducing a generalized seizure in the underlying brain regions. Patients receiving ECT are first sedated with general anesthesia and a muscle relaxant, the latter inhibiting convulsions so that seizure activity is only occurring in the brain while the body remains relaxed. Seizures last from 1 to 6 seconds and repeat treatments are typically done three times weekly for 6-12 treatments total over 2 to 4 weeks.

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WhatSZ IN THIS EDITION

SCHIZOPHRENIA SURVIVORS

Kit Wallis

Overcoming Schizoaffective Disorder and Thriving in Recovery

SchizoKitzo
Making the Uncomfortable, Comfortable

I have not become the plastic surgeon I dreamed of becoming throughout most of my life. However, in 2021, I began my own YouTube channel to encourage and educate others struggling with schizoaffective disorder/ schizophrenia, called **"SchizoKitzo."** My channel now has over 30,000 subscribers. It is not the life I had dreamed of, but I do find myself helping and even saving others, just in a different way because sometimes, that's how life works.

~ Kit Wallis

I was born in Winston-Salem, North Carolina in 1995. I had one younger brother, and we lived with my parents. As a child, I took piano lessons and appreciated art.

I was 14 years old when I heard voices for the first time. In the beginning, there was a voice in my mind called Twilight. He became my best friend, and we did everything together. Soon, he was joined by another, and then a third and a fourth, and so on. These Voices became my regular experience, and I became used to having friends in my head, which I didn't see as a problem. They assisted me with school and exams, and even helped me with any anxiety attacks. But the real challenge was my depression. It resulted in me learning to keep the voices a secret and drowning myself in books to hide from reality.

The thing that kept bringing me back was my unshakable dream to become a plastic surgeon. It was my dream since I was 7 years old, when I was introduced to the charity Operation Smile. Everything in my life revolved around saving people who had been born with cleft palate and other birth defects. This dream pushed me to do better in school. I kept a high GPA, and I labored to shadow as many doctors as possible, even in high school, keeping up with extra-curriculars to appear well-rounded.

But at age 17, I became profoundly suicidal, and struggled tremendously with self-harm as a way to cope. At home, things were tense between my mother and me. My parents had recently divorced, and neither of them listened to me when it came to my mental health. I suffered through it unmedicated. My life was miserable, and I struggled every single day to choose to keep living. But when everything seemed bleak, I would remind myself that I would be a resident one day, wearing a white coat adorned with my name in the embroidered black script: Kit Wallis, MD. That had such a nice ring to it.

But as one might have guessed by now, life had other plans for me.

My dream school was the University of North Carolina at Chapel Hill. I declared a biology major (pre-med) with an art history minor. While in college full-time, I would also work as a lab technician.

Fortunately, when I turned 18, I was able to go to a psychiatrist, and he diagnosed me with cyclothymia, a mild form of bipolar disorder. I didn't realize the "voices" were voices. I thought that I was thinking in conversation and didn't mention them. My doctor put me on Lamictal, a drug that would treat the depression that plagued me, saving my life.

However, the cognitive symptoms of my illness were starting to take a toll. Even on medication, I still had regular mood episodes. I would have around four defined bipolar episodes a year, and they would involve cycling between the hypomanic highs and depressive lows. They made completing coursework difficult. While I could enjoy the hypomania and get a lot done, I was burning through the neurons in my brain every time it happened.

Over these years, I went from having a near-photographic memory to barely being able to keep up with lectures. My depression – which returned and got worse throughout college – made it hard to work on homework and go to class, and life was becoming more complex. I still thought I could be a doctor, so I trudged forward. This goal is what kept me breathing. But I would graduate with a 3.05, and my dream of becoming a doctor was beginning to look unrealistic.

About this time, I started reading the Bible and attending church, and when I prayed to God, He often talked back. Unfortunately, the hallucination I called God told me the people I loved were going to die. My role was to watch it happen and not be able to do anything to stop it. Over time, I started feeling things weren't quite right. God wasn't lining up with what I knew from religion, so maybe it wasn't real. And the voices? Maybe they were hallucinations. Perhaps I was psychotic.

In the winter after I graduated from college, I got help from a call with my psychiatrist. He put me on an antipsychotic and would later diagnose me with the bipolar form of schizoaffective disorder. It was a scary moment to say the least, but it was also a new beginning.

Following college, I moved to New York, where I attended EMT school from 2018-2019, and finished with a 95% on my certification exam. However, during this year, I struggled with my mental health every day. I tried to study for the MCAT to revive my dream of going to medical school, but was unsuccessful. Finally, I moved back to North Carolina to look for a job, and found lab technician jobs paid much more than I would earn as an EMT. I was hired by Wake Forest University School of Medicine, a day before the lab was closed due to COVID, and I began working full-time from home. At this time, I also took a class in Dialectical Behavioral Therapy which was key in my journey to recovery.

I was promoted at my job to lab manager in 2022.

Today, my hobby is "cosplay" (making costumes) and I travel widely to attend cosplay conventions around the country. My life is filled with friends from cosplay and from college, and I am very close to both of my parents. In December, I will travel with my dad to Scotland.

CureSZ News

Schizophrenia: Reflections as a Sister and a Psychiatrist

Megan Good, *MD*
Early Course Psychosis Fellow
Harvard Medical School,Beth Israel Deaconness Medical Center

"Your sister is hearing voices. Could it be anything else?" It was 2017 and my exasperated father was asking me, his medical student daughter, to provide a non-psychiatric explanation for the auditory hallucinations my sister was experiencing. But deep down he knew the source of his daughter's distress. We all knew. My sister was experiencing a psychotic break, the first of many in her long journey with schizophrenia. Feeling helpless, I offered my support the only way a desperate medical student knows how: I read every book and article I could find about schizophrenia.

What began as a personal crusade to help my sister quickly evolved into a robust clinical and academic interest. This passion led me to psychiatry residency and, currently, a fellowship in early-course psychosis at Harvard Medical School and Beth Israel Deaconess Medical Center. I hope to spend my medical career treating patients with schizophrenia – a vocation that I consider to be my life's purpose. The combination of my lived experience and my professional accolades provides me with a unique view of schizophrenia, psychosis treatment, and the opportunity to advocate for my patients. With my sister's permission, I will reflect on my journey as both a sister and a psychiatrist.

Heredity is a curious thing. Some families pass down blonde hair, color blindness, or dimples. Members of my family tend to inherit mental illness. Bipolar disorder, schizophrenia, obsessive-compulsive disorder, alcoholism, suicide, and depression speckle the branches of our family tree. *"Crazy runs in the family,"* my dad once wryly explained. This is a chaotic pattern of inheritance I've noticed in my own patients as well.

I've spent many sleepless nights wondering, *"Why her?"* There is seemingly no rhyme or reason for the strange way that schizophrenia selects its patients. I naively thought that mental illness would spare a vibrant, considerate person like my sister. Why did fate choose her to carry this heavy burden? This is only one of the *"whys"* of schizophrenia that never seems to leave my mind.

Despite decades of research, we do not fully understand schizophrenia's direct cause, genetic involvement, or why treatment course varies. We will not procure answers to these questions without well-funded research endeavors. As my mentor, Dr. Matcheri Keshavan, says, *"We need data."* I have a deep appreciation for clinical research and biological psychiatry. I believe these disciplines will eventually lead to our understanding of psychotic illness and aid in the development of effective treatments that fully address both symptoms and patient quality of life. Families like yours (and mine) want and deserve answers.

Despite these uncertainties, I am hopeful. The recent development of medications that work differently than traditional antipsychotics (one newly FDA-approved) bring patients much-needed treatment options. These new medications work on a different system in the brain and are theorized to have less side effects than antipsychotics. Research focus and drug development have shifted focus to address the deficits in higher-level thinking, memory, social ability, and motivation that often accompany psychotic illness. Both medication and behavioral means such as cognitive enhancement therapy (CET) address these symptoms. Patients, families, and professionals alike will attest to the great extent to which these symptoms inhibit social and occupational functioning. Addressing them is crucial. Ultimately, treatment options should not only alleviate symptoms, but also improve patients' quality of life.

Clozapine is the gold standard medication for treatment-resistant schizophrenia. Unfortunately, due to extensive monitoring and frequent lab work, it can be difficult to access for patients in certain areas of the country. CURESZ's advocacy work to expand patient access to clozapine is helping to address a disparity in the psychiatric healthcare system. I have seen the numerous benefits of clozapine in patients and in my own sister. Shortly after starting clozapine, my sister started reading again. There was a long period in her illness where she could not focus long enough to do so. Now she returns from the library, her arms overflowing with books, excited to tell me about the latest dystopian novel she finished. I thought for sure that schizophrenia had robbed my sister of her favorite hobby, but this was simply not the case.

The manner in which I measure clinical success in my patients is two-fold. As a scientifically-minded physician, I measure progress through rating scales and lab results. As a sister and a clinician, I measure treatment success in meaningful moments and personal goals achieved. In my patients' experience, clozapine seems to produce both.

My sister remains my first and most personal reason to spend my life caring for patients with schizophrenia and other psychotic disorders. My role as her sister greatly informs my practice as a psychiatrist. My greatest hope is that these roles will combine to create a humanistic and scientifically-informed style of practice to better serve my patients. Simply put:

To me, this is personal.

~ Megan Good

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Treatment Resistant Depression

(continued from page 1)

For many patients, the effects of ECT are not sustained without maintenance treatment, which can be a single treatment done every 2-4 weeks after the initial 6-12 treatments. While the changes in the brain after ECT are not well understood, it is believed that seizure activity increases activity at serotonin receptors and increases the amounts of dopamine and norepinephrine available. ECT is more invasive than ketamine treatment or TMS, because of the risks associated with general anesthesia and cognitive impairments (memory, executive function, attention) which usually persist up to 6 months following the completion of treatment.

What Happens in Your Brain

We are still trying to understand what is happening in the brain of those with treatment resistant depression. Studies suggest that patients with TRD are unique, in that they have markers of increased inflammation and immune dysregulation compared with patients without TRD. Like antidepressants in non-TRD, TRD treatments appear to increase neuroplasticity in ways that repair connectivity between neurons in brain regions important in the regulation of mood. Antidepressant medications are thought to work through modulation of monoamines, neurotransmitters derived from amino acids, including dopamine, serotonin, and norepinephrine, that regulate brain processes such as emotion, motivation, arousal, and cognition. While the treatments for TRD likely have some effect on monoamines, their primary mechanisms of action rely on interaction with pathways that are not affected by antidepressants.

Getting Back Your Life

Unfortunately, depression is often insufficiently treated until this brain disorder has resulted in significant and negative impacts on a person's sense of self, ability to function and overall sense of wellness.

However, there is hope. As scientists and doctors better understand depressive disorders, including treatment resistant depression, a patient's illness will be diagnosed as early as possible for the best possible outcome. From psychotherapy to medication to brain stimulation, many patients with TRD are getting their lives back and moving on with the things that they love. Today, there has never been as much hope as there is now for TRD.

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Your contribution will help provide education and referrals to persons with schizophrenia, their families, and those who work with the seriously mentally ill. CURESZ informs the general public to better understand this serious brain disorder, and to provide scientific advances showing that there is hope for recovery, and a return to a fulfilling and normal life. The CURESZ Foundation is a 501(c)(3) nonprofit organization. All contributions are tax deductible.

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