

Neuromodulation Therapies for Schizophrenia

Of all the major psychiatric disorders (excluding dementia), schizophrenia is the one most thought of as a brain disorder. Alterations in brain anatomy, function and electrical activity have received more attention in schizophrenia than in any mood, anxiety and personality disorders. A common pattern in medical research is that emerging neuroscience technologies are quickly applied to the study of schizophrenia, often well before they are used to study other disorders. It is surprising, then, that neuromodulation treatments have not been more applied in schizophrenia.

When we speak of neuromodulation, it is not obvious what we mean. After all, many things influence (modulate) neurons. Neuromodulation refers to increasing or decreasing (modulating) brain function without using drugs or psychotherapy. Mostly this means increasing or decreasing (modulating) the overall activity of part of the brain by using energy. Many forms of energy are being investigated, but electrical and electromagnetic energy have been used the most.

Schizophrenia is treated primarily with antipsychotic drugs, which are beneficial but have limitations. For example, we have little control over where these medications act in the brain. In certain brain regions, antipsychotic drugs act to reduce symptoms, but in other regions they result in side effects. Most neuromodulation techniques can target specific regions of the brain, potentially bringing benefit without the problematic side effects caused by antipsychotic medications.

Almost 100 years ago, it was observed that some symptoms of mental illness improved after patients with epilepsy had seizures. Purposely inducing seizures also seemed to improve symptoms. After several years of trying various methods for inducing seizures, applying an alternating current to the side of the head emerged as the safest and most



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reliable method. Electroconvulsive therapy (ECT) is the first neuromodulation treatment that is still used today. It is highly effective in treating catatonia, depression and mania, though only occasionally is effective for the usual symptoms of schizophrenia. However, it may more be effective in schizophrenia when added to clozapine, when there is insufficient response to clozapine.

As soon as electricity was harnessed in the 1700's, physicians and others attempted to treat illness and enhance well-being by applying electric current. Although these practices were widespread in the 1800's, by the mid-1900's most electricity-based treatments were considered ineffective. However, newer studies show that simple electric stimulation can in fact treat psychiatric illness and enhance

function. The most popular approach is transcortical direct current stimulation (tDCS). Direct current is applied to the skull using two electrodes, increasing activity in the brain region under one electrode and decreasing activity in the brain region under the other electrode. The technology is simple, devices are sold for \$100-200, and no prescription is needed to get a device. See below for potential uses in schizophrenia.

Electric stimulation of the brain is inefficient, in that most of the energy is diverted by scalp and skull, so only some of the energy makes it to the brain. Magnetic energy can affect brain tissue in the same way as electricity, but that energy is not diminished by passing through the patient's scalp and skull. Magnetic stimuli can be used to induce seizures (magnetic seizure therapy might eventually replace electroconvulsive therapy), but magnetic energy is mostly used to modulate the activity of particular brain regions. This is transcranial magnetic stimulation (TMS). TMS is FDA-approved for treating major depressive disorder and obsessive-compulsive disorder, but has no current FDA approved indications in schizophrenia. However, studies so far suggest that TMS may help with several aspects of schizophrenia, as described below.

Rather than transmitting directly to the surface of the brain, electric stimuli can also modulate brain activity by stimulating cranial nerves. For example, when peripheral branches of the vagus nerve (the tenth cranial nerve) and trigeminal nerve (the fifth cranial nerve) are stimulated, these impulses are carried by those nerves to the brain. The easiest way to do this is around the ear, where both the trigeminal and vagus have branches. Although there are reasons that vagal nerve stimulation might help in schizophrenia, there has been little research on cranial nerve stimulation in schizophrenia so far (Corsi-Zuelli et al 2017).

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SCHIZOPHRENIA SURVIVORS



The Story of Chelsea Kowal

Chelsea was born in 1989 in Newark, NJ, the last of three children. She experienced a difficult childhood filled with abuse and neglect.

At age fifteen, Chelsea was suicidal, which resulted in her first hospitalization, and would be only one of many. At age twenty-five, Chelsea's oldest brother committed suicide. She was only seventeen. Her remaining brother was diagnosed with severe mental illness during her early adulthood years.

As a teenager, Chelsea and her mother were evicted and became homeless. Chelsea dealt with her homelessness and abusive upbringing by directing all her effort toward her studies, and remained drug and alcohol free, after seeing how abusing these substances took a toll on her family.

Despite her unstable family situation and unpredictable mental health, Chelsea was ambitious for her future, and settled on attending the Syracuse University to major in bioengineering, starting in 2007.

Despite great success in school and work, during the beginning of her junior year, Chelsea's abusive upbringing came back to haunt her. Unable to think clearly, she attempted to take her own life by jumping off a forty-foot building. Fortunately, a large tree braced her fall, and though she had broken her back, she survived. After two days of hospitalization, she was able to walk again, which friends and family considered to be a miracle. She would wear a body brace for the next three months to allow her broken vertebrae to heal.

Despite repeated hospitalizations, Chelsea graduated from college in 2012. She decided her next step was to study for a PhD degree in biomedical engineering, and applied to the University of Florida, where she received a full tuition scholarship to attend, starting the fall of 2012.

However, during the beginning of her graduate studies, she began to experience her first clinical hallucinations and delusions. She expected to win a Nobel Peace Prize. In and out of the hospital in Florida throughout her degree program, her diagnosis was changed to schizoaffective disorder, bipolar type. At one point, a physician told her it was impossible for her to finish graduate school, and she should not even try. Despite the voices and delusions, Chelsea successfully graduated with her Master's degree in biomedical engineering in December of 2013 with A's and B's.

Following her graduation, her psychosis returned, worse than it had ever been. She would not work again for ten years.

She returned to New Jersey and entered a partial care program through the local psychiatric hospital while living at home with her mother. In 2017, Chelsea was finally admitted for a long term stay at Greystone

Park Psychiatric Hospital, where she would live for almost two years, until August of 2019.

Upon her discharge, she was still acutely symptomatic and delusional, believing she was the President of the United States, and believing she was Christ, returning to earth. Chelsea also believed she was working for the FBI, CIA, DOJ, etc. (basically every government agency there is).

After being hospitalized again about a year after being discharged, Chelsea finally accepted and made peace with her psychiatric diagnoses. It was at that time when a doctor prescribed a new medication, clozapine.

Chelsea began clozapine in fall of 2020. After one month, she saw a significant reduction in her voices and delusions which she had never imagined possible. She recalls her voices were reduced from constantly to about 5% of the time.

Within a few months, Chelsea had gained a high enough level of recovery to grasp a firm hold of her dream of working again, and began a new life. She began a job in January of 2021 for the National STEM Honor Society (Science, Technology, Engineering and Mathematics) helping students increase their awareness of STEM fields. In January of 2022 she resigned from her job, focusing instead on the training she needed to become a peer support specialist.

Today, Chelsea has been in nearly full recovery for two and a half years. In recovery, she finds herself busy again. She volunteers as a peer support specialist and a recovery coach in training. She also currently volunteers at her local library and YMCA, as well as a few other organizations. She currently suffers no side effects and also experiences very limited symptoms. After years of hearing voices all day long, today, she still usually hears voices about 5% of the time, which allows her to stabilize mentally enough to use coping skills to deal with the remaining voices.

Clozapine was different than any other medication she tried, as every other medication either was ineffective, intolerable, or stopped working after a few months.

Chelsea reflects that *"Clozapine totally changed my life and enabled me to move forward in ways I never thought I could again... Now, I want my life to matter, especially because I nearly died a few times in my life. I am just grateful to be alive. Every day is a blessing."*

She recalls choosing Biomedical Engineering because there are so many projects in the field that would allow her to make a difference in the world. Her dream is to continue to make a difference in the lives of as many people as she can.

Chelsea recently became engaged to be married, and is looking forward to all that life has to offer.



Chelsea Kowal has lived with schizophrenia since beginning college. Despite several hospitalizations and refractory symptoms, she is now recovered on clozapine. She graduated with her master's degree in biomedical engineering in 2013, and is currently applying to PhD programs to continue her study of engineering.

CLOZAPINE SIDE EFFECTS

WORTH THE RISKS

Henry A. Nasrallah, MD and Richard Sanders, MD

Clozapine is a unique medication, with higher efficacy than all the other antipsychotic medicines for patients with treatment resistant schizophrenia, but can be more difficult to manage.

It's true that clozapine can have serious physical side effects, and that certain rare side effects can be life-threatening. What's most important: according to published longitudinal studies, **patients with treatment resistant schizophrenia receiving clozapine have a lower mortality from medical conditions or suicide than those treated with other antipsychotic medications.** This isn't because clozapine has a better safety profile than the other antipsychotics.

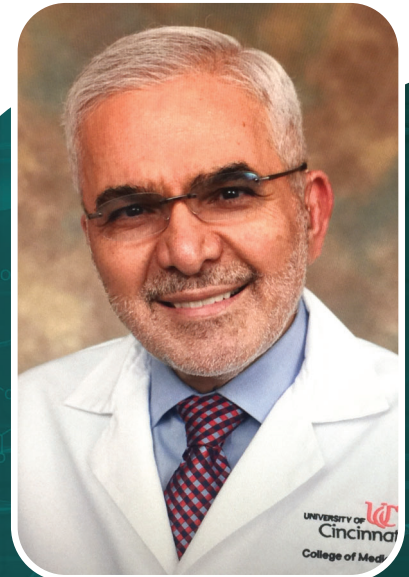
People taking clozapine live longer because it works better against psychosis.

Clozapine's serious side effects are uncommon. For example, the weekly blood test will tell you if you are in danger of developing neutropenia (a white blood cell drop) which happens in only 1% of patients, and the medication can be discontinued without any danger. Because of this, the risk of death from clozapine-induced neutropenia happens about 1 in 10,000 people worldwide, and even less in the U.S. due to better monitoring. The risk of seizures is uncertain but is higher than the 1% risk of seizures with other antipsychotic medicines. Seizure risk is related to higher clozapine dose, but this is typically an easily managed adverse effect. Death due to clozapine-related seizures is very rare. Inflammation of the heart muscle (myocarditis) occurs in 1%-3% of people starting clozapine during the initial 6 weeks of treatment, but less often when the dose is increased slowly. Many doctors check serum troponin and CRP (a blood test that reflects inflammation), every week for the 1st 6 weeks of treatment at the same time the patient undergoes lab tests for neutropenia. Pneumonia occurs in 2-3% of people in the first 2 months of starting clozapine, and may be related to an unusual side effect, sialorrhea (i.e. drooling). Drooling

usually happens during sleep (people find a wet pillow in the morning) but can happen while awake. This is treated by reducing the dose and/or using one of several medications (oral atropine drops, or Botox injections in the salivary glands) that slow down saliva production. Pneumonia does not require that clozapine be stopped, but the dose may need to be lowered temporarily until drooling problems are better managed. Constipation can become a serious problem to the extent that the FDA issued an advisory in January 2020 warning about the use of clozapine with other anticholinergic medicines that slow gastrointestinal motility. Those combinations can cause a severe problem (ileus). When starting clozapine, doctors usually prescribe a stool softener (docusate), and then add other medications (e.g. polyethylene glycol-3350, bisacodyl, linaclotide etc.) to prevent extreme constipation and ileus.

Weight gain and sedation are common side effects, but they are rarely dangerous. Metformin, a widely used diabetes pill is often used to help prevent weight gain due to clozapine, and is started when clozapine is started. The new glucagon-like peptide-1 agonists (e.g. semaglutide) have FDA approval for obesity in nondiabetics, and have been studied in clozapine treated patients to help manage weight gain. Sedation can be short-lived or persistent, and it can be mild or a real hindrance. It can be addressed in a variety of ways including the administration of a waking medication like modafinil. Doctors should regularly check weights as well as lab tests, and should ask patients about side effects at every visit.

Clozapine is worth the risks, especially when managed carefully, as treatment resistant patients have no viable effective medication alternatives. It is the only antipsychotic medication that can restore mental wellness in patients who otherwise would remain disabled for the rest of their lives with intractable hallucinations and delusions. It is more likely to prolong than to shorten lives. It is also more likely than other antipsychotic medications to enable patients with severe schizophrenia to function vocationally and socially, and improve their quality of life.



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Neuromodulation Therapies for Schizophrenia *(continued from page 1)*

The ultimate in modulating specific brain areas is deep brain stimulation (DBS). Tiny electrodes are placed by neurosurgeons into very specific regions. This approach is most often used to treat the tremor of Parkinson's disease, but it's also used to treat other movement disorders and obsessive-compulsive disorder. Many studies in depression have produced variable results so far. There have been few attempts to treat schizophrenia with DBS (Corripio et al 2022). Where would we place the electrodes? There are many types of symptoms to treat in schizophrenia, each of which may involve very different parts of the brain. Now I will describe some results using neuromodulation to treat the specific symptoms seen in schizophrenia.

Auditory hallucinations, usually the perception of voices, are a major problem in schizophrenia. When hearing real or hallucinated voices, the superior temporal gyrus (Wernicke's area) is activated. Thus, researchers attempted to treat auditory hallucinations by using tDCS to reduce activity in this brain region. Initial results were encouraging, but later studies have not shown consistent benefit.

Negative symptoms are often the most debilitating symptoms of schizophrenia. Negative symptoms are those features of human experience that are diminished in patients with schizophrenia. These include emotional experiences, motivation, non-verbal communication and social interest. Antipsychotic drugs are better at treating positive symptoms than negative symptoms, which is probably why researchers focus on negative symptoms with drug-free neuromodulation treatments. For example, an under-active dorsolateral prefrontal cortex is associated with negative symptoms and may be targets for neuromodulation treatments. So far, studies show that increasing activity in the left dorsolateral prefrontal cortex reduces negative symptoms. Both tDCS and TMS seem to bring this benefit (Tseng et al 2022).

Lack of insight isn't a diagnostic criterion for schizophrenia, but it is very common and interferes with recovery. If you don't believe that you are ill, you likely will not see the benefit of treatment. Looked at as a group, tDCS studies which activate the dorsolateral prefrontal cortex (or inhibit activity in temporoparietal cortex, as many of these studies did at the same time) may improve insight to some extent (Adam et al 2022). If this holds up in future studies, neuromodulation could help many people in achieving recovery from schizophrenia.

The desire to improve cognitive performance has driven many neuromodulation studies, almost all of them using tDCS. Small studies have found benefits in school-based learning, learning

certain job-specific skills, and enhancing video game performance. People with schizophrenia tend to have problems with certain aspects of cognition; not usually severe enough to be obvious, but enough to interfere with functioning. Studies of schizophrenia and other brain disorders are only beginning, but there is evidence of some cognitive enhancement when tDCS is combined with cognitive training (Burton et al 2022).

Another common problem in schizophrenia is substance use, which aggravates many of the other symptoms of schizophrenia. The few studies looking at the use of TMS suggest that stimulating the left dorsolateral prefrontal cortex helps subjects crave less and use less (Johnstone et al 2022). There haven't been enough studies using tDCS to test its efficacy in treating substance use disorders in schizophrenia.

Neuromodulation approaches for schizophrenia may provide promising future directions for treatment, but research has lagged behind the studies of neuromodulation for depression and anxiety disorders. So far, it seems that using TMS or tDCS to stimulate the left dorsolateral prefrontal cortex may help with negative symptoms, insight, cognition and drug use. Using neuromodulation to reduce activation in the superior temporal gyrus might help decrease auditory hallucinations. However, to make progress in the use of neuromodulation as a treatment for schizophrenia, the scientific and medical communities need to better understand exactly how brain function is different in schizophrenia. This enormous effort continues.

References:

1. Adam, Ondine, et al. "Efficacy of Transcranial Direct Current Stimulation to Improve Insight in Patients With Schizophrenia: A Systematic Review and Meta-analysis of Randomized Controlled Trials." *Schizophrenia Bulletin* 48.6 (2022): 1284-1294.
2. Burton, Cynthia Z., et al. "Combined Cognitive Training and Transcranial Direct Current Stimulation in Neuropsychiatric Disorders: A Systematic Review and Meta-Analysis." *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging* (2022).
3. Corripio, Iluminada, et al. "Target selection for deep brain stimulation in treatment resistant schizophrenia." *Progress in Neuro-Psychopharmacology and Biological Psychiatry* 112 (2022): 110436.
4. Corsi-Zuelli, Fabiana Maria das Graças, et al. "Neuroimmune interactions in schizophrenia: focus on vagus nerve stimulation and activation of the alpha-7 nicotinic acetylcholine receptor." *Frontiers in immunology* 8 (2017): 618.
5. Johnstone, Samantha, et al. "Neuromodulation to treat substance use disorders in people with schizophrenia and other psychoses: A systematic review." *Frontiers in psychiatry* 13 (2022): 77.
6. Tseng, Ping-Tao, et al. "Assessment of noninvasive brain stimulation interventions for negative symptoms of schizophrenia: a systematic review and network meta-analysis." *JAMA psychiatry* (2022).

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