DANIEL HORAN

Daniel Horan was miserable until magnetic brain stimulation helped him get his life back on track.

THERAPEUTICS

Negative feedback

Schizophrenia debilitates not just by psychosis but by depriving people of the ability to feel pleasure.

BY ELIE DOLGIN

Daniel Horan was 20 years old and studying to be a chemical engineer at the University of New Hampshire in Durham when he started to believe he had the power to read minds. He was also hearing voices and had an elevated sense of self-importance. After a confrontation with his roommate in 1998 — around the time that Horan believed he was "the devil in hell surrounded by fallen angels" — Horan was suspended from the university. Psychiatrists soon diagnosed him with schizophrenia.

Horan started taking an antipsychotic drug called risperidone, which made him go from feeling "sky high" to "extremely depressed", he recalls. Blaming the emotional downturn on the drugs, he stopped taking the risperidone. His delusions soon returned and he was hospitalized again. Horan switched medications to another antipsychotic called olanzapine. Once more, he felt a lack of motivation and even suicidal thoughts. He stopped taking the olanzapine but soon found himself at an in-patient psychiatric centre.

Throughout these episodes in and out of the hospital, Horan assumed that his blunted emotions and lack of motivation were simply side effects of the antipsychotic drug therapy. He was wrong. Such 'negative' symptoms are actually an integral and primary feature of the disease, experienced by around 20% of people with schizophrenia. "Everyone talks about the positive symptoms — the hallucinations, the delusions and the paranoia," says Horan, now 36 and an auctioneer selling antique clocks and watches in Windham, New Hampshire. "I didn't realize there was another side to schizophrenia."

Flat affect, social withdrawal, inability to feel pleasure — these are often a huge barrier preventing people with schizophrenia from living independently, holding down jobs, establishing personal relationships or managing everyday social situations. But there are no existing therapies, pharmaceutical or otherwise, that are approved to treat the negative symptoms of schizophrenia.

"We have very little that we're able to offer patients for these symptoms," admits Steven Zalcman, head of the Clinical Neuroscience Research Branch at the US National Institute of Mental Health in Rockville, Maryland. Antidepressants are better than nothing, but the benefit they provide is usually modest at best.

Fortunately, new therapeutic options could be on the way. Horan, for his part, recently participated in a clinical trial designed to test whether a non-invasive magnetic brain-stimulation technique could help with the negative symptoms of his disease. Others are involved in studies evaluating new drugs or innovative forms of psychosocial treatment.

Success with one of more of these therapies in mitigating the recalcitrant negative symptoms of schizophrenia should dramatically enhance the total management of the disease, says Stephen Marder, director of the Section on Psychosis at the University of California, Los Angeles, Neuropsychiatric Institute. "It would transform treatment."

NO GOOD

The arrival of a new class of 'atypical' antipsychotics in the late 1980s was supposed to solve the problem of negative symptoms. But as Horan's experience shows, these drugs were not the solution. Indeed, despite early reports of benefit, subsequent meta-analyses and well-controlled trials showed no reduction in primary negative symptoms from these agents.

Over the years, many other types of medication have been examined as potential adjunct treatments for negative symptoms. Nearly all have failed. The most recent drug flops came from Targacept in Winston-Salem, North Carolina, and from the Swiss pharmaceutical giant Roche. Each had experimental compounds in mid- or late-stage development for what many considered to be the two most promising drug targets for controlling negative symptoms. In recent months, each released trial data showing that their drugs proved no better than placebo pills.

Results like these "make the task of finding truly novel treatments for negative symptoms of schizophrenia that much more daunting", says Jeffrey Lieberman, psychiatrist in chief at New York Presbyterian Hospital–Columbia University Medical Center in New York. Yet even though the specific drugs may have had their flaws, Lieberman doesn't think the targets are necessarily the wrong ones. "We must persevere," he says.

The target pursued by Targacept was the alpha-7 nicotinic acetylcholine receptor, which is activated by the neurotransmitter acetylcholine and by nicotine. Studies show that individuals with schizophrenia have serious

reductions in alpha-7 receptors in several regions of the brain. Many people with schizophrenia overcome their lack of alpha-7 receptors by smoking cigarettes — often heavily.

Research has found that some schizophrenia patients smoke to self-medicate, as it relieves their negative symptoms. Nicotine is hardly an ideal therapeutic agent, however. As well as the health risks of smoking, nicotine is an addictive substance to which people develop tolerance. This limits the long-term benefits of nicotine and it's why scientists have been working on less toxic and more chronically effective treatments that make alpha-7 receptors more responsive to naturally occurring acetylcholine.

The proof-of-principle that activating the alpha-7 receptor with a small-molecule drug could ameliorate negative symptoms came from Robert Freedman, a psychiatrist at the University of Colorado School of Medicine in Aurora. Freedman and his colleagues ran a trial that involved 31 people with schizophrenia who received either placebo pills or twice-a-day doses of DMXB-A, which is a partial agonist of the alpha-7 receptor[1]. The researchers expected the treatment to improve cognitive impairments associated with schizophrenia, such as trouble focusing or problems with working memory, but they observed more consistent benefits in negative symptoms.

Targacept initially saw the same effect with its activator of the alpha-7 receptor. In a 12-week, 185-person trial led by Lieberman, treatment with the Targacept drug led to significant improvements in negative symptoms compared with placebo[2]. But in a 477-person follow-up study, the drug offered no such benefit. Targacept officials announced the failed trial results in December 2013.

TRICKY BUSINESS

Despite the clinical setback, Lieberman still sees potential in activating the alpha-7 receptor. "It's a viable target," he says, "but it's very tricky to engineer a compound that will be optimally effective." Freedman agrees. He thinks Targacept's once-a-day drug was probably too strong and long acting. Thus it engaged the alpha-7 receptor but did not disassociate fast enough, leading to a diminished response known as desensitization.

Although drug companies generally prefer to make once-a-day pills, patients in this setting might need to take shorter-acting drugs more often. "Maybe this therapeutic principle will work best if you get a couple of good hits of drug a day," says Freedman, who is now running an 80-person trial testing DMXB-A given four times per day. A handful of other companies have alpha-7 activators in various stages of clinical development, but they are all now being pursued primarily for cognitive enhancement, rather than to alleviate negative symptoms, says Harry Tracy, the editor and publisher of *NeuroPerspective*, a monthly publication focused on treatments for neurological and psychiatric diseases.

Roche, meanwhile, was banking on a different therapeutic target: the glycine transporter 1 (GlyT1) protein found on glial cells in the brain. When the protein is blocked, more of the amino acid glycine stays in the synapse. The glycine then activates NMDA (*N*-methyl-D-aspartate) receptors, which are involved in the signalling of glutamate, an excitatory neurotransmitter that's deficient in people with schizophrenia and is thought to underlie many of the negative and other symptoms of the disease.

In 2010, Roche presented data from a 323-person, phase II trial demonstrating improvements in the negative symptoms of participants who took the company's experimental GlyT1 inhibitor bitopertin for eight weeks rather than a placebo pill[3]. Decision Resources Group, a market-research firm in Burlington, Massachusetts, started to forecast blockbuster sales for the agent. But in January 2014, Roche dropped a bombshell. The company released top-line results for two of the three pivotal follow-up trials designed to test bitopertin's impact on negative symptoms. In both phase III studies, adding bitopertin to antipsychotic therapy for 24 weeks did not significantly reduce negative symptoms compared with placebo.

As *Nature* went to press, Roche was awaiting data from its remaining studies — one focused on predominant negative symptoms, three others on suboptimally controlled positive symptoms — before deciding the fate of bitopertin. A few other drug companies are also pursuing different ways of modulating glutamate signalling to combat negative symptoms.

NOW WE'RE TALKING

With pharmacological efforts to treat negative symptoms facing so many stumbling blocks, a number of researchers have begun to test non-drug interventions. These include forms of psychological techniques used more commonly by mental-health professionals in other disease settings, such as cognitive behavioural therapy and social skills training, as well as less traditional methods, including art therapy and so-called loving-kindness meditation.

Ann Kring and her colleagues at the University of California, Berkeley, recently surveyed the literature on psychosocial therapies for negative symptoms[4]. Although empirical data are limited, the researchers concluded that these treatment techniques hold promise as add-ons to medications. "Negative symptoms are an area where psychosocial treatments could be a wonderful adjunct," Kring says.

So could brain stimulation. In December 2013, as part of a clinical trial at the Beth Israel Deaconess Medical Center in Boston, Massachusetts, Horan received ten treatments over five days of transcranial magnetic stimulation. This brain-activating therapy involves placing an electromagnetic coil above the scalp and releasing magnetic pulses that cause nerve cells to fire. By altering the wiring of dysfunctional neural networks, this treatment, when administered over the left prefrontal cortex to people with schizophrenia, has been shown to moderately alleviate negative symptoms[5]. Now, a team led by neurologist Alvaro Pascual-Leone at Beth Israel Deaconess is testing whether such stimulation works even better when directed at the cerebellum, a brain region involved with regulating emotion and its display.

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In a preliminary, eight-person trial[6], the therapy proved "revolutionary" for some participants, says Mark Halko, one of Pascual-Leone's colleagues. One woman, he says, "went from living at home to living independently, holding down a job, making friends — all things she didn't do before the trial." In the follow-up trial, which involves a sham treatment to test for a placebo effect, similar dramatic responses can be seen in participants like Horan. After the first few treatments with magnetic stimulation, "it was like a miracle," says Horan, who learned after-the-fact that he received the real treatment during the trial. "I had verve, pep, enthusiasm."

The treatment wasn't a cure, though. In the months after the trial, the beneficial effects gradually started to wear off for Horan. The technique is approved in the United States only as a treatment for major depression or migraine headaches. But fortunately for Horan, his doctors agreed to continue administering the therapy off-label. In March 2014, Horan received six more sessions of brain stimulation over three days at Beth Israel Deaconess. Although "less intense" than his first experience, Horan says, "there was definitely an improvement."

After years of working part time and receiving disability benefits from the government, Horan can now see a future where he's self-sufficient. He's even trying to buy out his business partner at the auction house. The magnetic stimulation "gives me a little glimmer of hope that I might at least have the health I need," Horan says. "It's given me a new lease on life." ■

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