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Are Scientists Closing In on Treatments for Schizophrenia's Most Elusive Symptoms?

By Bill Myers

Researchers, buoyed by a spike in promising clinical trials and tools, believe they may be close to unraveling new ways to treat some of the most insidious yet elusive effects of schizophrenia.

Scientists have long divided schizophrenia according to its so-called positive and negative symptoms. "Positive" signs are the most obvious and familiar– the hallucinations and delusions. The "negative" ones are more subtle — and harder to treat. They're things like apathy, the inability to feel any emotion and disorganized thinking — symptoms that tend to hide in plain sight.

Decades of research into treatments, especially for the mental disorder's "negative" effects, have turned up empty, leaving scientists discouraged and patients out of options. But now, for the first time in years, many longtime researchers say it looks like the tide may be turning.

"There's been this slow but steady effort, on the part of the whole industry, both to redouble our efforts to find new treatments but also, perhaps, a little renaissance, if you will, in our thinking about how to evaluate negative symptoms," says Mark Opler, chief research officer at MedAvante-ProPhase. "The cautious optimism springs out of these small signs of hope."

There are currently 177 active trials worldwide on potential targets or therapies for schizophrenia's negative symptoms, according to the FDA. That's the most in recent memory, Opler says — and certainly in the four years since Roche announced that its once-promising drug bitopertin — a glycine uptake inhibitor then being considered as an adjunct to antipsychotics for the treatment of persistent negative and poorly controlled positive symptoms — flunked its Phase II trials.

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After bitopertin's failure, trials for drugs to ease negative symptoms seemed to go into eclipse, Opler says. But two years later, researchers led by Sonia Dollfus of Centre Hospitalier Universitaire de Caen in France published the results of a study based on analysis of negative symptoms from an unlikely source: the patients themselves.

The team created the Self-evaluation of Negative Symptoms (SNS) survey, which made sure that questionnaires were consumer-friendly enough for patients to complete themselves (sans clinician input or interviews) and, also, that the info they provided was specific enough for researchers to mine for clues.

The researchers tested the easy-to-use self-assessment tool on 49 patients with either schizophrenia or schizoaffective disorder (a chronic mental health condition characterized by schizophrenia-like symptoms)–and the results were very promising, says John Krystal, a psychiatrist and professor at Yale School of Medicine.

"People have believed that problems with the assessment of negative symptoms may have undermined the ability to detect meaningful clinical changes in this aspect of the illness. It is likely that this [SNS] scale will be more highly correlated with other self-rated assessments related to quality of life than are the clinician-rated results," says Krystal.

Though encouraged, he cautioned that "it remains to be seen" whether the SNS will lead to development of new meds.

But experts agree this field is overdue for a breakthrough after a long dry spell. The last drug the FDA approved on this front was clozapinein the late 1980s.

The stakes are enormous because negative symptoms are often the first sign that something has gone wrong in the brain, says Remy Luthringer, executive chairman and CEO of Minerva Neurosciences. Perhaps worse, they tend to linger even after "positive" symptoms have waned, he notes.

"Everybody recognizes that negative symptoms are what are keeping these patients [from] functioning or family life," Luthringer says. "Nothing has worked until recently."

Minerva last year sponsored a Phase II trial on a drug called MIN-101, an amino acid derivative, to see if it could help allay schizophrenia's negative symptoms. Some 244 European patients were hospitalized

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and taken off antipsychotic and psychotropic drugs before being given either a placebo or MIN-101 daily for 12 weeks. The findings, published in the *American Journal of Psychiatry*: The ones who took the drug showed "statistically significant improvement." Minerva is now recruiting for a Phase III MIN-101 trial, according to the FDA.

In an ironic twist, part of the recent optimism comes from a seemingly vexing insight — that negative symptoms aren't exclusive to schizophrenia. People with other conditions like Alzheimer's and Parkinson's disease as well as those recovering from a stroke also often report feeling apathetic or un-motivated.

That suggests scientists may be looking at "a behavioral syndrome," British researchers Masud Husain and Jonathan Roiser say in the most recent issue of *Nature*. Drug tests on mice and rats "have revealed the complexity of neurotransmitter involvement in motivated behavior," they write. "This seems an area ripe for investigation, given the clear clinical need and close correspondence between behavioral tests developed for human and animal models."

And it may be that the dearth of successful trials since clozapine hit the market will help yet by giving the industry "a better sense of what doesn't work," MedAvante's Opler says.

"It's too soon to tell yet whether this is the beginning of another renaissance," he adds. "But I don't think it's an accident that we're suddenly seeing so much creativity in assessments and so much creativity in the search for new molecules."