DEEP DIVE

Why don’t we have better drugs for autism?

BY **RACHEL ZAMZOW**

15 FEBRUARY 2017

Photography by Vanessa McKeown

Taylor Stevenson’s family never left him out of conversations, but they never expected him to participate, either. His contributions, if he made any, were a few random words — gibberish or a Big Bird quote.

So when Taylor started speaking his mind in his squeaky, singsongy voice, his mother, Debbie Stevenson, was stunned. “It was such a huge shock,” Stevenson says. She cried tears of joy. This was in late 2012, when Taylor was 16. Over the next year, his once-cursory answers spun into three- to five-word sentences. Phrases such as “I’m okay, thank you” became part of his repertoire.

Taylor has **fragile X syndrome**, a genetic condition that causes lifelong intellectual disability. One in three people with the syndrome also have autism. Taylor is not one of them, but he does have some autism-like features, such as difficulties with language. At first, Stevenson wasn’t sure what was triggering her son’s changing behavior. Perhaps Taylor’s new high school had sparked the improvement, or perhaps the countless hours of intensive therapy he had endured were finally paying off.

Stevenson began to suspect that a new drug Taylor was taking was responsible. A few months earlier, Taylor had enrolled in a clinical trial exploring the effects of an experimental drug called mavoglurant, manufactured by the pharmaceutical giant **Novartis**, for people with fragile X syndrome. Stevenson had heard about the trial through her volunteer fundraising work with the nonprofit **FRAXA Research Foundation**, a fragile X research and advocacy organization. Because there are no approved drugs to treat fragile X, she eagerly signed Taylor up.

Taylor enrolled in the 12-week trial in September 2012 and began taking either mavoglurant or an inactive placebo twice a day. (Neither the Stevensons nor the researchers knew which drug Taylor was taking.) The family flew from their New York City home down to Atlanta, Georgia, once a

month for questionnaires and behavioral testing at Emory University, one of the trial's 38 sites.

Within a few months, Stevenson noticed a slight shift in Taylor's behavior. He started asking her for help when he needed it, and his anxiety diminished. These improvements persisted even after he switched to the second, long-term phase, during which he and the other participants took mavoglurant for more than a year. Stevenson became convinced that Taylor's improvement really was due to the drug.

To Stevenson's surprise, however, rumors that the trial wasn't going well began to spread through FRAXA circles in February 2014. When the family showed up at Emory for another testing session a few months later, the researchers told them Novartis was suspending the trial. "I was beyond shocked," Stevenson says. "I thought that even if only 25 percent of the population has seen what I've seen, of course they'll approve it — because we have nothing else."

When Taylor's supply of the drug ran out, his strides forward reversed. Within a few months, his sentences diminished to single words, and now he mostly ignores questions, as he did before the trial.

Stevenson, who took Taylor's regression the hardest, wished the study had been able to capture Taylor's progress. But it would become clear to her that the trial had been poised to fail even before it got off the ground. Deeper issues — the wrong design and inadequate tests — crippled the study from the start. For the families who heard about the trial's failure in June 2014 via FRAXA, this revelation came as a shock. "I was pretty horrified," Stevenson says. "Do we have a drug that is getting slammed because we didn't measure this properly?"

As it turns out, this trial's misfire wasn't an isolated incident. The same problems have dogged major trials exploring three of the most promising drugs for fragile X, including ventures launched within the past decade by **Roche** and the now-defunct **Seaside Therapeutics**. Stunted by flawed designs, each of the trials flopped, and by late 2014 all three drugs had been yanked from the research pipeline. To date, no drugs are approved to treat fragile X syndrome.

In the case of autism, too, few drugs have **proven effective** in trials, and several have failed due to poor design. Just two drugs, risperidone and aripiprazole, are approved by the U.S. Food and Drug Administration (FDA) for autism and are intended to relieve irritability. A few others treat attention deficit hyperactivity disorder and **epilepsy**, which often accompany autism. But none have passed muster for treating the condition's core social impairments or **repetitive behaviors**.

For example, in 1998 a preliminary report suggested that the gut hormone secretin boosts the language abilities of children with autism. But the excitement fizzled when larger studies **did not confirm those findings**. Experts also proposed that antidepressants such as citalopram and

fluoxetine would reduce repetitive behaviors in children with autism, but clinical trials of these ideas **did not show improvements**.

This series of disappointments has left families like the Stevensons with limited options. Most people with autism or fragile X **rely on behavioral therapy**. In desperation, others **end up trying alternative treatments** such as **marijuana**, which lack scientific support. Stevenson says she fears the high-profile failures will discourage families from participating in clinical trials.

Problems with study design and improper measures have continued to plague autism clinical trials, leading to the deaths of once-promising drugs. Many of these studies also continue to test drugs in broad groups of participants, a practice that is inappropriate for conditions as heterogeneous as autism and fragile X, says **Eric London**, director of the Autism Treatment Research Laboratory at the New York State Institute for Basic Research in Developmental Disabilities. “That’s the number one reason drug trials fail,” he says.

But a new way of approaching drug research has started to shift this pattern of failure and frustration. In an attempt to overhaul autism clinical trials, scientists have teamed up with partners in industry and federal agencies to create better study designs and smarter ways to cluster participants and measure their symptoms. They hope to redesign how trials are done.

“It’s very possible that we could have drugs that work really well on development, and we’ve missed them.” Elizabeth Berry-Kravis

Trial and error:

In the early 2000s, a small community of researchers sought to try and curb the symptoms of fragile X syndrome by offsetting its primary mechanism. The **mutations that cause fragile X** lower the supply of a protein called FMRP, and some mutations cause people to lack FMRP altogether. This releases a brake on the production of other proteins, causing them to be produced in excess at **synapses**, the sites where neurons interact. The surplus of these proteins disrupts neuronal connections, and is thought to underlie the learning difficulties and behavioral features of fragile X.

The researchers thought that blocking a protein called mGluR5, which counters the normal role of FMRP, might restore the balance of synaptic proteins in people with fragile X syndrome. To their delight, the idea worked — in mice. A string of studies showed that in mouse models of fragile X, mGluR5 blockers **normalize synapse function and improve learning**. More than 30 papers thus far have shown the benefits of mGluR5 blockers in animal models, says **Elizabeth Berry-Kravis**, professor of pediatrics, neurological sciences and biochemistry at Rush University in Chicago. “That’s one of the biggest bodies of basic science evidence for a mechanism ever amassed.”

Emboldened by this bulk of evidence, several drug companies launched clinical trials in people with fragile X syndrome. In 2009, a 12-person trial sponsored by Neuropharm Ltd., a U.K.-based company now owned by **Autism Therapeutics**, found that an mGluR5 blocker called fenobam **eases oversensitivity to sounds**, a common feature in people with fragile X. That same year, Novartis' mavoglurant **showed early promise** for treating hyperactivity, social difficulties and repetitive behavior in seven people with fragile X who lack FMRP. And an early Roche-sponsored trial, which also began in 2009, found that the drug basimglurant, another mGluR5 blocker, seemed to alleviate anxiety.

However, as Novartis and Roche prepared to launch much larger trials to test these drugs further, Berry-Kravis, who ran studies at Rush for both companies, grew concerned. The drugs target connections between neurons, which have the most capacity for change during early brain development, so they should work best in children. But both proposed trials were focused on adults and adolescents, which is the typical first step for large clinical trials. If these trials failed to show a benefit, the chances that the companies would launch studies in children were slim, Berry-Kravis says.. (The companies ran early studies to test the drugs' safety in children but didn't include children in larger trials.)

Berry-Kravis also had reservations about how the companies planned to judge the drugs' effectiveness. The FDA requires companies to specify these so-called 'outcome measures' before a trial begins. Novartis decided to rely on the Aberrant Behavior Checklist (ABC), a questionnaire that asks parents to rate their child's problem behaviors, including irritability and hyperactivity. Some participants in an earlier mavoglurant trial had improved **on the ABC**, and the test had also been the measurement of choice in trials of risperidone and aripiprazole.

The FDA's approval of those two drugs made the ABC a logical choice for future trials, says Florian von Raison, therapeutic area head for Novartis, who led the company's later mavoglurant trials. Roche also included the ABC in its trials of basimglurant, though it picked an anxiety survey as its primary measure. A spokesperson from Roche declined to comment on the trials.

However, a behavioral test might not be the best measure of drugs that affect communication between brain cells, notes Berry-Kravis. The greatest benefit, if any, would probably be **related to cognition and learning**, she says, so outcome measures should ideally track how well participants pick up new skills or language abilities.

Walter Kaufmann, who was involved in research for both mGluR5 trials, says he had similar doubts based on his own research. He was also collecting data for trials of arbaclofen, a drug Seaside Therapeutics had tested since 2008 for people with fragile X and, later, for those with autism. The company had chosen the ABC as its goalpost, but researchers leading the studies had begun to suspect that the measure didn't detect the behavioral changes, such as gains in language, they saw in the participants. Results from later trials for both conditions showed that the drug didn't shift participants' ABC scores any more than the placebos did. (In May 2013, Seaside

announced plans to **terminate its arbaclofen studies**, and the company subsequently went under.) With the mGluR5 inhibitor studies, “we were in some way repeating the same mistakes from the arbaclofen trial,” says Kaufmann, director of the Center for Translational Research at the Greenwood Genetic Center in South Carolina. “It was a very unfortunate situation.”

The researchers voiced their concerns about the trials’ design to Novartis and Roche, but the companies wouldn’t budge. Beginning in 2010, hundreds of adults and teens, including Taylor, enrolled in the trials. During each study session, the participants’ parents completed the ABC and several other questionnaires, gauging traits such as social impairment and anxiety. But none of the measures seemed to capture Taylor’s extraordinary progress. Stevenson was concerned. “All those amazing things I had just seen in the last month and then I’d told the clinicians about at Emory, none of it translated to what I was putting down on this piece of paper,” Stevenson says.

When the results of the trials rolled in, Stevenson’s fears were confirmed. The effects of the drugs did not differ from placebo based on the ABC or any of the other behavioral measures. In the eyes of the drug companies, the trials had failed. Novartis announced plans to **shut down development of mavoglurant** in April 2014, and Roche shuttered its program five months later. Families like the Stevensons were left empty-handed.

Limiting factors:

The failure of these trials, with their repetition of earlier mistakes, is a source of enormous frustration for scientists. “It’s very possible that we could have drugs that work really well on development, and we’ve missed them because of the way we develop drugs,” Berry-Kravis says.

As with the ABC, many measures are ill-equipped to track shifts in key autism features in response to the drug being tested, experts say. Panels of researchers **convened to evaluate existing measures** for this purpose and could recommend only a few — such as the Vineland Adaptive Behavior Scales, a test of social, communication and daily living skills — and even those were suggested with reservations. Other assessments used in some trials, such as the Autism Diagnostic Observation Schedule, are designed to diagnose autism or measure its overall severity, not necessarily to detect behavioral changes over time, says **Gahan Pandina**, senior director of neuroscience at Janssen Research and Development. The ABC and many other tests are completed by parents, whose ratings of the effects may be **swayed by their hopes**.

These limitations leave researchers without the precise, sensitive measures needed to capture subtle changes in language or social interaction in response to drugs. Mavoglurant was helping Taylor, but the ABC couldn’t detect it, even when it was scored using modified criteria designed to be more **sensitive to fragile X symptoms**, such as hyperactivity and social withdrawal.

Given the weaknesses of traditional questionnaires, some researchers are turning to brain waves and other biological signals to identify potential responders. Many drug studies now include **biomarkers** such as **eye tracking**, electroencephalography (EEG) and levels of various molecules in the blood, says **Craig Erickson**, associate professor of psychiatry at Cincinnati Children's Hospital Medical Center in Ohio. Erickson is using some of these biomarkers in ongoing trials of the drug acamprosate, which is thought to block mGluR5, in people with **autism** or **fragile X syndrome**.

"We call it the bells-and-whistles approach, but I think it's what we need to do to really discover what are these drugs doing and whom do they potentially help the most," Erickson says.

Researchers may also need to adopt unconventional trial designs to tease out drug effects. Some experts propose **N-of-1 trials**, in which researchers or families carefully track the effects of a drug in a single person. This approach keeps the focus on whether the drug improves the lives of individual people, as opposed to a broad and heterogeneous group of participants, says **Randall Carpenter**, chief scientific officer of the Rett Syndrome Research Trust, a funding organization based in Connecticut. (Carpenter previously co-founded Seaside Therapeutics.) "As many people have said, 'If you've seen one child with autism, you've seen one child with autism,'" he says. "We need to start treating it that way."

"I thought that even if only 25 percent of the population has seen what I've seen, of course they'll approve it." Debbie Stevenson

Forging forward:

Learning from the long string of failures, autism researchers are collaborating with drug companies and federal agencies to revamp the way clinical trials are conducted.

One team of researchers spanning multiple centers has embarked on a $28 million initiative to put autism measures and biomarkers through rigorous testing. In this project, called the **Autism Biomarkers Consortium for Clinical Trials**, the researchers plan to follow 200 children with autism for six months and carefully chart their behavior and brain functioning with a specific set of candidate biomarkers. The four-year project, which began recruiting in October, aims to provide a **set of measures** that can precisely detect changes in trial participants. These tools may help researchers better track how participants respond to treatments, as well as predict who is most likely to benefit, says lead researcher **James McPartland,** associate professor of child psychiatry and psychology at the Yale Child Study Center. As a bonus, when the project ends, its five sites will be equipped to run high-quality trials.

Taking a different approach, researchers at Janssen Research and Development are creating a web-based and mobile application for parents to record aspects of their children's behavior, from mood to moments of social engagement. The idea is to help parents gather rich information for researchers in an easier and more comprehensive way than traditional paper-and-pencil questionnaires, says Pandina, the project's leader. Janssen is also developing wearable sensors to track sleep and repetitive movements, much like a fitness tracker logs steps. Pandina hopes to hone these components, which are still undergoing initial testing, into a standardized system that can be shipped off for use in clinical trials.

Another project, launched in 2012 in Europe, aims in part to pinpoint subtypes of autism. The nearly 30 million euro (about $32 million) endeavor, called European Autism Interventions – A Multicentre Study for Developing New Medications (**EU-AIMS**), merges the efforts of academic researchers and industry players such as Roche and Pfizer. In one piece of the five-year project, researchers are tracking about 450 children with autism for up to two years, collecting detailed genetic, brain imaging and behavioral data, to help define meaningful subgroups of individuals.

EU-AIMS and the Autism Biomarkers Consortium are both working with government agencies such as the FDA in the hopes of finding biomarkers that the **regulators are more likely to accept**. This way, drug companies will have more objective measures than the questionnaires, such as the ABC, that have previously been used, McPartland says. "It will put us in a position of being proactive instead of reactive," he says.

These efforts may bolster plans to revive some of the drugs from the failed trials: Arbaclofen is slated for new autism trials funded by the Simons Foundation (*Spectrum*'s parent organization). A new study led by researchers at the Children's Hospital of Philadelphia aims to test arbaclofen with a measure of brain activity, as opposed to traditional questionnaires such as the ABC. The researchers plan to examine the drug's effects using a technique called magnetoencephalography — which maps magnetic signals produced by neurons — to predict who might respond to the drug in subsequent trials.

Mavoglurant is also getting a reboot. Berry-Kravis plans to launch a new trial in June that she hopes will address **the flaws** of previous studies. The study, sponsored by the U.S. National Institutes of Health, will involve children, because the drug is expected to affect how the brain establishes connections. In addition to tracking behavior with questionnaires, Berry-Kravis and her colleagues plan to observe how well the participants respond to a language-training program while taking mavoglurant or an inactive placebo for six months. They also plan to test mavoglurant's effects on brain functioning using eye tracking and EEG.

This is the trial Berry-Kravis had envisioned from the beginning: one that may pick up on improvements in learning or behavior — a few extra words, a meaningful response — and one that

might have caught the gains Stevenson had seen in her son. Taylor, now 20, is too old to participate in the new trial, but Stevenson says she wouldn't hesitate to enroll him in future studies. She says she still believes in the power of research, and helps FRAXA raise funds for new studies. "Clinical trials are huge," she says. "We need them."

Taylor still uses words sparingly and fixates on unusual things, such as the compact discs that go into his beloved portable DVD player. But he likes being around other people and making them laugh with a funny look or a non sequitur. He lives at a residential school for people with disabilities on farmland a couple of hours away from his family's home in New York City. In November, he moved into the adult house at the school, and Stevenson drove up to help him get settled. "It's huge, because this is where he could really stay for the rest of his life," she says.

Given all of his difficulties, Taylor may need a whole cocktail of drugs, Stevenson says, and so may many others like him. The trick will be getting enough drugs on the market to try out different combinations. In the meantime, she is open to anything that might help her son navigate his world, like his new adult program. Everyday skills, such as brushing his teeth and cooking himself dinner, are still challenging for Taylor. Learning little things like this, she says, would dramatically change his life.