

MEDICINE

Early studies show promise for drugs that treat the social impairments of Fragile X and other, more common forms of a crippling disorder

# New science, fresh hope for autism patients

BY JULIE STEENHUYSEN

REUTERS/JOSHUA LOTT

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**L**ynn and Neil Balter always dreaded stage productions at their son Jack's elementary school.

When Jack was up there with the other performers, the noise, the lights, the crowd almost always got to him, and he would "start spinning," wandering around the stage or turning in circles, Lynn says. "It usually turned into an embarrassing situation," she adds.

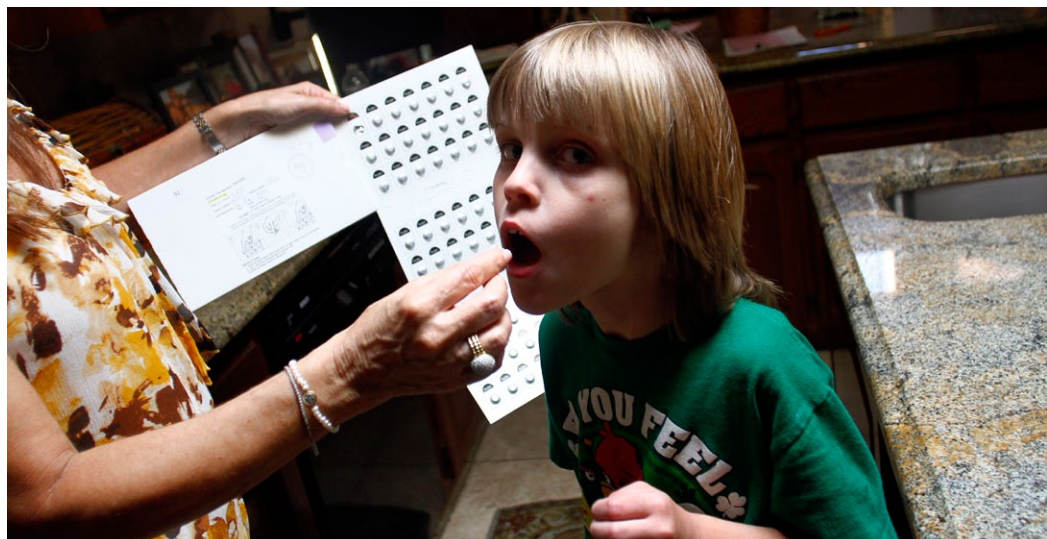
But at a dance performance at Jack's Scottsdale, Arizona, school last December, something was different. "He was half a beat behind in the dance, but he did the whole thing," Neil says. "He participated and took the bow with his class."

Afterward, Jack's teacher greeted the Balters in tears. "I don't know what is going on with this kid, but there is this miracle happening and I have a different kid at school," she told the Balters.

Jack, 9 years old, has autism. What his teacher didn't know is that Jack was taking part in a clinical trial for a drug aimed at overcoming some of the social impairment associated with autism, a spectrum of disorders that range from the social awkwardness and narrow interests seen in Asperger syndrome to severe communication and intellectual disabilities.

For years the best that doctors have been able to offer patients with autism is intensive therapy and anti-psychotic drugs such as Johnson & Johnson's Risperdal to blunt some of the extreme behaviors associated with their disorder – tantrums, aggression and self-harm. Anti-psychotics quiet the patients. But they do nothing to address the core social and communication problems that make it impossible for many autistic children to develop deep relationships with their families and peers and grow into independently functioning adults.

As Jack's experience suggests, that may be about to change. Researchers are conducting advanced trials of the first drugs expressly



designed to correct the genetically induced signaling problems in the brain that result in autism. The early indications are positive enough to offer new hope for families and spark interest from drug companies.

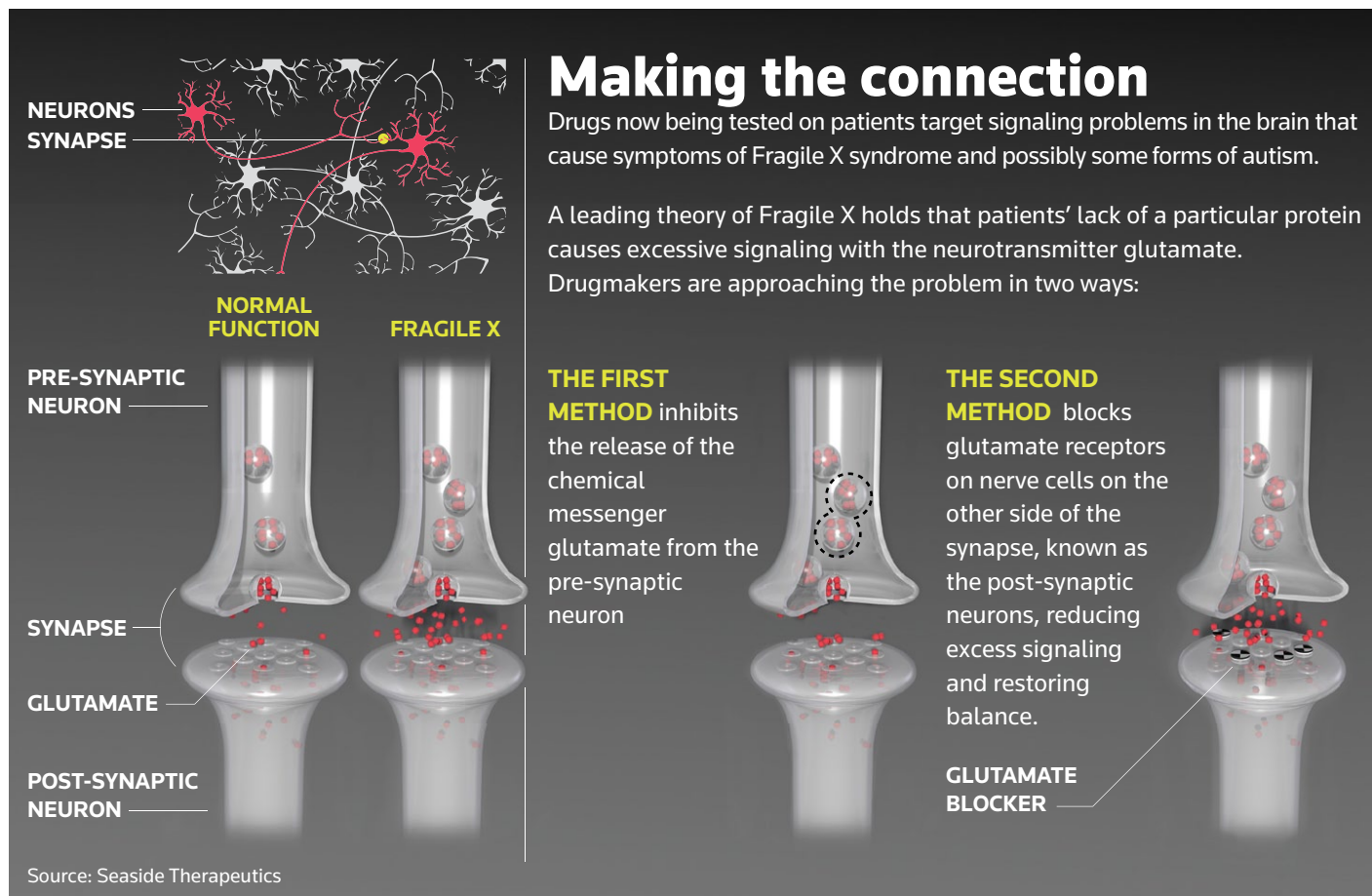
For patients, this research "may not solve their autism, but it may solve aggression, it may solve sensory overload, which leads to a lot of behavioral issues," says Isaac Pes-sah, an autism researcher at the University of California at Davis, who has not been involved in any of the drug trials.

Swiss drugmakers Novartis International AG and Roche Holding AG, as well as privately held Seaside Therapeutics in Cambridge, Massachusetts, all have drugs in late-stage tests targeting Fragile X syndrome, the most common form of inherited intellectual disability and the most common known genetic cause of autism. And though Fragile X accounts for only a small percentage of autism patients, early studies suggest the drugs may work in other forms of autism, too.

If the current trials show enough benefit to satisfy U.S. regulators, the first drugs could be available in a few years. And if that happens, they will serve a growing population. The latest figures from the Centers for Disease Control and Prevention estimate that as many as 1 in 88 children in the

**VISIBLE DIFFERENCE:** When 9-year-old autism patient Jack Balter (this page and preceding page) enrolled in a study of Seaside Therapeutics' drug arbaclofen, his parents and teachers noticed improvements almost immediately. **REUTERS/JOSHUA LOTT**





United States has autism, a near-doubling of the rate reported in 2002.

Even so, the number of studies of the drugs remains small, and the trials themselves have been relatively small. Of those that have been completed, the effect has been dramatic in some patients but negligible in others.

“This is a new day, and that’s exciting,” says Dr. Thomas Insel, director of the National Institute of Mental Health in Bethesda, Maryland, one of the National Institutes of Health. “But we also have to temper that with the reality that there may be many failures along the way before we come up with a treatment that is both effective and safe.”

As a toddler, Jack Balter was hyperactive. He would be mesmerized by the wheels on toy trucks or anything else that spins, stand

on his tiptoes, cover his ears – all classic signs of autism. “We didn’t even know what autism really was, so we didn’t know it was something out of the ordinary,” says Lynn, 52.

Jack was diagnosed with autism just before his third birthday. Since then he has had about 60 hours of intensive therapy a week, including speech and physical therapy and social interaction therapy. About 10 percent of autistic children who receive intensive therapy “bloom,” enjoying rapid improve-

Even with therapy, Jack has struggled to interact with the world around him, talking in numbing detail about his favorite subjects, never playing sports or watching cartoons, standing too close to people.

ment as they grow older, according to a recent study published in the journal *Pediatrics*.

“We’ve been lucky. He’s responded,” says Lynn. Jack is now in a mainstream classroom with a full-time aide.

In a family video posted to YouTube, Jack lays out his ambitions: “On the outside, I’m just a regular old kid. On the inside, I’m a mad scientist.” He says that when he grows up, he wants to be an oceanographer, a meteorologist, a climatologist, a volcanologist and a seismologist.

But even with therapy, Jack has struggled to interact with the world around him, talking in numbing detail about his favorite subjects, never playing sports or watching cartoons, standing too close to people. To other children, he seems odd.

“He’s always been in his own tunnel,” Lynn says.

Last November, Jack was enrolled in a trial of Seaside's compound STX209, or arbaclofen. Arbaclofen contains one of the active ingredients in an older drug, baclofen, that has been used since the 1960s to treat cerebral palsy.

Jack was part of a randomized study of 150 children with autism. Neither his parents nor his doctors knew whether he received the drug or a placebo.

Jack's parents are convinced he got the drug. Neil, 51, who founded custom storage maker California Closets at age 17 and now runs another custom closet and home organization business, graphed Jack's progress during the trial. "You can see when he got to the 10-milligram dose, 18 days in a row" he came home with a positive report from his teacher, Neil says.

Teachers didn't know about the trial, but they knew something was suddenly different. Carrie Cunningham, Jack's third-grade teacher, says Jack was more focused and could express himself better, and his emotions were mostly in check. "His aide and I both noticed a change almost immediately," she says.

They also noticed when the study ended. "It was a nightmare," Cunningham says. "All of a sudden, everything brought tears to his eyes. Everything was a battle."

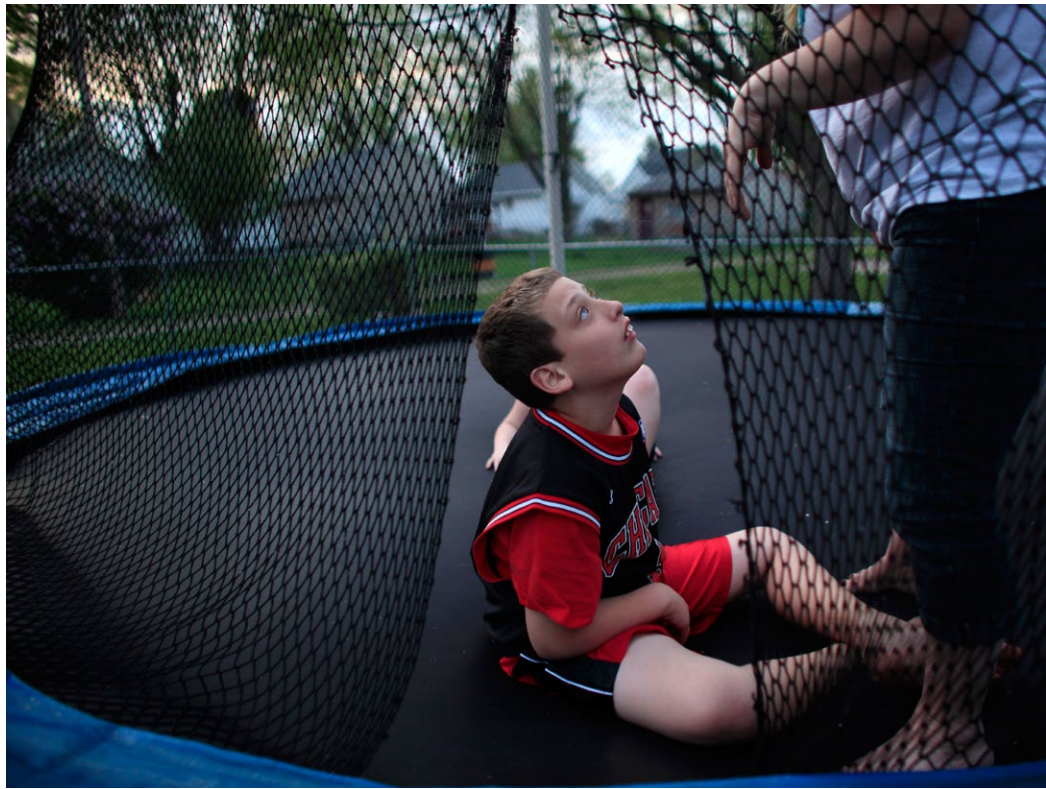
Two weeks later, Jack started on a follow-up study in which his parents know he is getting the drug, and Jack has once again improved.

Neil says that on a scale of 1 to 10, with 1 being severe disability and 10 being normal, he used to think of Jack as a 5. Since Jack has been taking arbaclofen, Neil sees him at 7.5.

"It's not a cure," he says, "but it definitely moved the needle."

Seaside is running two late-stage trials in adults and children with Fragile X, and a study in children with different types of autism, including autism with no identifiable cause, like Jack's. Results of the study in which Jack participated are expected later this year.

For decades scientists believed genetic



BROADER HORIZONS: After two years on arbaclofen, Parker Roos is able to enjoy sports and play time with friends and family. **REUTERS/JIM YOUNG**

diseases of brain development resulted in permanent disability. "The mindset was, 'Damn. This is a real shame. ... You are faced with a lifetime of managing the symptoms as best you can,'" says Mark Bear, a neuroscientist at the Massachusetts Institute of Technology and co-founder of Seaside Therapeutics.

As a result, drug treatments have focused on behavior control. The commonly prescribed drugs for autistic patients – antipsychotics such as Risperdal and Bristol-Myers Squibb Co's Abilify – calm tantrums and prevent patients from hurting themselves or others.

"People talk about Risperdal and Abilify as sort of chemical straitjackets," says Dr. Paul Wang, vice president of clinical development at Seaside Therapeutics. "They control problem behaviors, but they don't really improve the desired function of people with autism."

The work begun by Bear more than a decade ago has helped to change the approach to autism research.

Bear had been studying how learning affects the spaces, or synapses, between nerve cells, or neurons, when he made a key discovery about Fragile X.

Neurons communicate with one another across synapses via chemicals called neurotransmitters. Some neurotransmitters stimulate brain activity, others inhibit it. In a healthy brain, the two work in balance.

With Fragile X, this process is disrupted because the gene that creates the Fragile X Mental Retardation Protein, or FMRP, is not working. Bear and his colleagues proposed that the absence of FMRP led to excessive activity of the neurotransmitter glutamate in what is called the metabotropic glutamate receptor, or mGluR, pathway, resulting in the behaviors associated with Fragile X.

Thus, they posited, drugs that inhibit glutamate signaling might treat Fragile X and related disorders. Subsequent experiments showed that reducing the activity of glutamate alleviates Fragile X symptoms in both young and adult animals. “What these studies have shown is we can really get substantial benefit by correcting altered signaling,” says Bear, who also serves as a scientific adviser to Seaside Therapeutics.

When Bear first presented the idea that Fragile X could be corrected at a 1992 conference, many experts were skeptical. Now it is the prevailing theory behind treatments for Fragile X and is seen as a key to unlocking autism and other brain disorders.

“Many of the genes related to autism are right in the same pathway that has been implicated and worked out in Fragile X,” says Dr. Edwin Cook of the Autism Resource Center at Rush University Medical Center in Chicago, which is participating in the Seaside Therapeutics trials. “I don’t expect any medication to help everyone, but I think we have a good shot here.”

Seaside Therapeutics’ arbaclofen works by reducing the amount of glutamate available in the synapse. The experimental drug Novartis is testing works by a different mechanism; it blocks glutamate receptors on the surface of the neuron.

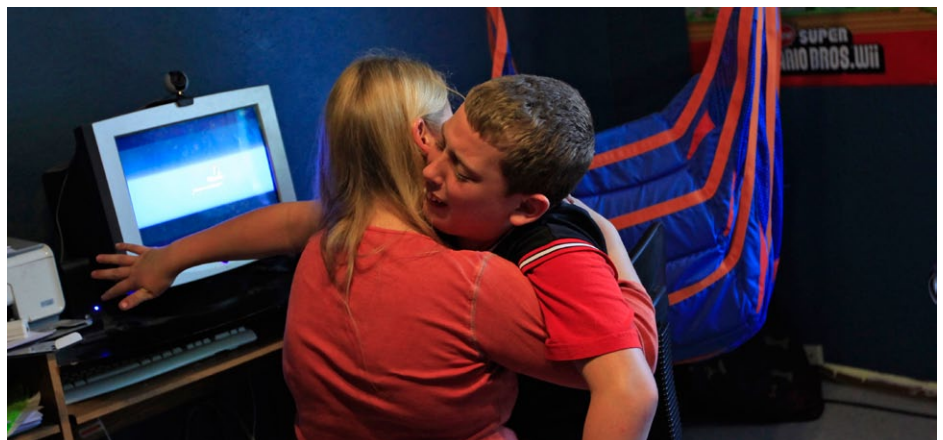
Novartis’s trial of its drug for Fragile X in 30 adults failed to show statistical significance. But in seven patients with the most severe form of Fragile X – those with a full mutation of the FMR1 gene – the drug showed significant reductions in hyperactivity and inappropriate speech. Novartis is now running a larger study in Fragile X, and it will test the drug for four months instead of one.

Roche also has a Fragile X drug that blocks glutamate receptors. It, too, is conducting advanced clinical trials in adults and adolescents with Fragile X.

Roche, along with advocacy group Autism Speaks and King’s College London, in March announced one of the largest-ever



**FAMILY MATTERS:** The parents of Jack Balter (tickled by his father, Neil) and Parker Roos (with his mother, Holly) are optimistic the new drugs will help their children grow into independently functioning adults. **REUTERS/JOSHUA LOTT/ JIM YOUNG**



academic-industry research projects to find new ways to develop drugs for autism. The \$39 million effort includes contributions from Roche, Eli Lilly & Co, Servier, J&J, Pfizer Inc and Vifor Pharma.

“The field is coming of age,” says Luca Santarelli, global head of Roche Neurosciences.

### GRIM PROGNOSIS

Holly Roos is a carrier of the genetic mutation that causes Fragile X, and both her son Parker, 12, and her daughter Allison, 9, have varying degrees of Fragile X.

Parker hit all the early developmental milestones – rolling over, sitting up, crawling and walking – but his fine motor and language skills stalled.

Holly, who worked in a child-care center near her home in Canton, Illinois, wasn’t reassured when doctors told her not to worry. Then, Holly’s mother, a nurse, attended a genetics conference in Chicago where she learned about Fragile X, and the pieces of the puzzle fell into place.

Tests showed that Parker had a full mutation in the FMR1 gene that causes Fragile X, meaning the gene was completely shut down and he was very likely to have both intellectual disability and autism.

A geneticist gave Holly the grim prognosis. Parker would live in an institution. He would never be toilet-trained. He would never go to school. He would never be independent. (His sister, like many fe-

males with Fragile X, is highly functional and shows scant impairment.)

Undaunted, Holly enrolled Parker, then 10, in one of Seaside's trials of arbaclofen for Fragile X patients. At the time, Parker could say only a few words. Instead of talking, he screamed. "He had a happy scream, and a sad scream, and an 'I want that' scream," Holly says.

School was an exercise in frustration. "If he had a rough day, he would lunge at me and bite and not let go. I had huge welts and really bad bruises on my legs and arms," Holly recalls.

Dr. Elizabeth Berry-Kravis, director of the Fragile X clinic at Rush University Medical Center, has been studying the disease for more than two decades. Parker, she says, "was a mess. He had tantrums. ... He was aggressive. He tried to knock you away."

In Parker's trial, 63 patients received either a placebo or arbaclofen for one month, and then they switched.

At first, nothing. Then, about two weeks after Parker switched drugs, he knocked a glass off the kitchen table. As Holly turned to pick up the shards, she heard her son say, "I am sorry, Mom. I love you."

It was the first time he had uttered those words, and they came out in complete sentences. "I waited 10 years to hear him say, 'I love you, Mom,'" Holly says.

Other families had similar breakthroughs, says Dr. Randall Carpenter, Seaside's president and chief executive officer.

Some noticed their children would hang out in the kitchen longer after they came home from school instead of holing up in their bedrooms. Others made new friends outside their special education groups for the first time. Teachers who knew nothing of the trial reported that children were more engaged in school.

But other test subjects showed only modest benefits or none at all, and the study failed to show a statistically significant ef-

7 patients with the most severe form of Fragile X showed significant reductions in hyperactivity and inappropriate speech.

fect. Berry-Kravis says the sample size was too small to demonstrate a benefit. She and others involved in the study also say it erred in choosing changes in irritability as its main goal. They say future trials will focus on the social withdrawal problems researchers are targeting with the new drugs.

Researchers say that given baclofen's record for safety as a treatment for cerebral palsy, Seaside's version of the drug, arbaclofen, may have a better chance of winning U.S. regulatory approval than it would if it were an entirely new compound.

Bear thinks it might be five years before any of the current drugs being tested are approved to treat Fragile X and other forms of autism. Berry-Kravis estimates 2014 at the earliest.

Until then, Jack, Parker and others helped by the medicine will be able to continue taking it through extension studies that will gather data on the long-term effects of arbaclofen.

## NOT A CURE

In the tight-knit autism and Fragile X communities, few expect a cure, but many hope the drugs under study will give patients a chance to lead more independent lives. Stories like those of the Balters and the Rooses feed the optimism.

Neil Balter recently took Jack to a basketball game. Jack watched the players and cheered his team on – instead of sit-

ting with his headphones on, playing video games, as he used to do.

Neil says he knows Jack is smart, but he wants more for his son: "I want him to have friends and have a life – to be socially accepted, to be able to get married. That is where I believe some of the benefit of arbaclofen comes in."

For Parker Roos, who has been on the drug for two years, the differences are even greater. He's now active in sports and is doing better in school.

Before, a trip to the park could set off violent tantrums. Recently he attended a birthday party – at a noisy game arcade – and for the first time, Holly didn't tag along. (She waited in the parking lot, just in case.)

When his Special Olympics basketball team made it to the state tournament in Normal, Illinois, 90 minutes from home, Parker stayed in a hotel with the rest of the team, one of the many things Holly never imagined would be possible.

Holly used to wear long-sleeve shirts year-round to conceal the bruises she got from tending to Parker. Now, with no bruises to hide, she wears T-shirts and shorts. On her left shoulder, Holly got a tattoo of a green X with the word "Fragile" written in black.

*Editing by John Blanton and Douglas Royalty*

## FOR MORE INFORMATION

**Julie Steenhuisen**

julie.steenhuisen@thomsonreuters.com

**John Blanton, Enterprise Desk Editor**

john.blanton@thomsonreuters.com

**Michael Williams, Global Enterprise Editor**

michael.j.williams@thomsonreuters.com