Carlos Rodriguez, 14, is one of 6,000 children in the Bronx who fall somewhere on the autism spectrum. (Photo by RIck Guidotti, Positive Exposure)

BY GARY GOLDENBERG

From cannabis to whipworms, scientifically promising treatments for autism are being tested at Einstein and Montefiore

Carlos Rodriguez of the Bronx seemed like a healthy, happy baby. But as his first birthday approached, he began to scream and cry at the slightest provocation. His “twos” were particularly terrible. While his peers were learning to talk, Carlos communicated only by grunting and pointing. Even worse, he would throw tantrums, banging his head against anything and everything.

The family’s pediatrician suspected a serious developmental problem and referred Carlos to Children’s Hospital at Montefiore. There he was diagnosed with autism spectrum disorder (ASD) and received the latest behavioral, educational, and medical therapies. The interventions got him talking, if sparingly, and enabled him to attend a mainstream school with special services.

Carlos has a loving home, a supportive school, and top-notch specialty care —yet these are not enough. Now 14, he avoids eye contact, can’t tolerate busy or noisy environments, doesn’t take part in sports, and abhors the slightest deviation from his daily routine. At home he prefers being alone in his room, watching YouTube videos and playing with Transformers, his favorite toys.

Six thousand children who live in the Bronx and another 12 million nationwide fall somewhere on the autism spectrum. Only a small percentage will successfully outgrow their diagnoses.

Carlos and his mom, Maribel, enjoy a day at a playground in the Bronx. (Photo by RIck Guidotti, Positive Exposure)

Filling the Treatment Void

The U.S. Food and Drug Administration (FDA) has approved only two drugs for ASD: the drugs risperidone and aripripazole, both for treating ASD-related irritability. But no treatments exist for the core symptoms of ASD: deficits in social interaction and communication, repetitive behaviors, restricted interests, and difficulty with new situations. That absence of therapies has created desperation.

“We know that parents are trying all kinds of alternative therapies on their children who have ASD,” says Eric Hollander, M.D., professor of psychiatry and behavioral sciences at Einstein and director of the Autism and Obsessive Compulsive Spectrum Program at Einstein and Montefiore. “One of our goals is to subject potential therapies to the rigor of solid scientific research so we can inform parents and clinicians about the therapies’ usefulness.”

For the past two decades, Dr. Hollander has been a national leader in the search for new ASD treatments. In research published in 2005, he and his colleagues were the first to assess fluoxetine (Prozac) for relief of ASD symptoms. Their placebo-controlled, double-blind trial, involving 45 children and adolescents with ASD, found that low-dose liquid Prozac was more effective than a placebo in reducing repetitive behaviors in particular and ASD-symptom severity in general. In a 2012 study, they found similar results in adults. Prozac is now one of the most commoly used treatments for ASD.

Dr. Eric Hollander, director of the Autism and Obsessive Compulsive Spectrum Program at Einstein and Montefiore

ASD

is a neurological condition that affects how people experience the world and interact with others

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"Prozac seemed worth investigating," Dr. Hollander says. "The drug influences brain levels of serotonin, and serotonin dysregulation appears to be common in people with ASD. Plus, Prozac and other SSRIs [selective serotonin reuptake inhibitors] are frontline treatments for disorders that—like ASD—can involve repetitive behaviors. But not all patients with ASD respond to Prozac, and not everyone tolerates it, so we decided to test other treatments."

Righting an Imbalance

Other treatments evaluated by Dr. Hollander's group include the hormone oxytocin; the antiepilepsy drug valproate; a marijuana extract; and the eggs of a parasite that infects pigs—diverse therapies that each address a widely accepted cause of ASD: an excitatory/inhibitory (E/I) imbalance in brain neural circuits.

Considerable evidence, from animal and human studies, suggests that ASD is accompanied by overexcitation of the brain's neural circuits, due to either an increase in excitatory neuron signaling or a decrease in inhibitory signaling.

"This E/I imbalance alters the way the brain processes information and regulates behavior," Dr. Hollander says. "The imbalance triggers seizures, and we believe it's also responsible for the core ASD symptoms that we can't treat effectively yet. So we look for interventions that show promise for correcting the E/I imbalance and, hopefully, easing the symptoms of people with ASD."

As his colleague Bonnie P. Taylor, Ph.D., assistant professor of psychiatry and behavioral sciences at Einstein, puts it: "We're open to testing therapies that look promising. New therapies for kids who have ASD are

urgently needed. So if there's a rationale for a treatment and we're confident that it's safe, we'll figure out a way to develop a trial."

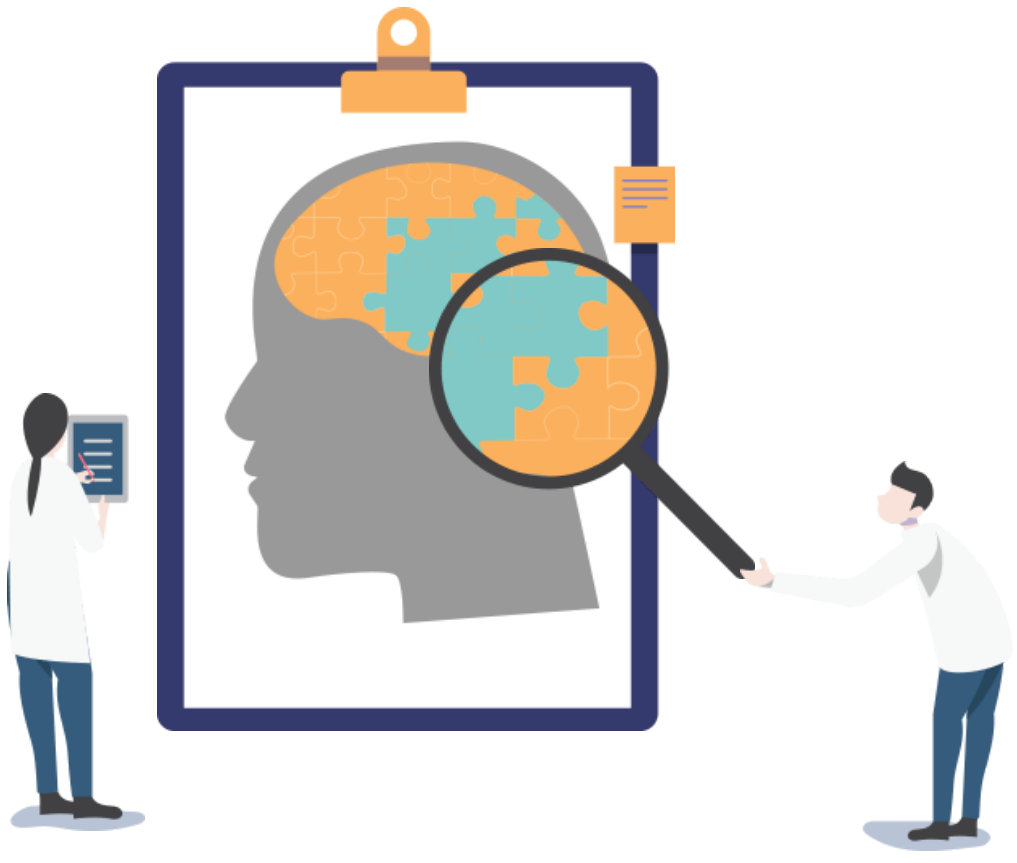
A child who has autism works on an IQ test at the Einstein campus under the supervision of Dr. Bonnie P. Taylor.

Easing Irritability

Risperidone and aripripazole have been approved by the FDA for treating irritability related to ASD. Both were originally approved as antipsychotic medications and can have serious side effects, including significant weight gain. Dr. Hollander realized that valproate, a drug approved for treating seizures in epilepsy, might be a better alternative.

For one thing, valproate may normalize the E/I balance, since it appears to work by raising levels of gamma aminobutyric acid, a neurotransmitter that inhibits neuron signaling in the brain. And in studies involving other conditions, the drug relieved symptoms also found in ASD—reducing aggression in people with borderline personality disorder, for example. Similar drugs have proved to be useful in treating disorders with repetitive and impulsive features, such as compulsive gambling and binge eating.

Dr. Hollander and his colleagues have conducted two randomized, placebo-controlled clinical trials assessing valproate's effectiveness in treating ASD patients, primarily children and adolescents. Both trials found that valproate was significantly more effective than a placebo in relieving repetitive behaviors and irritability and agitation in people with ASD. Valproate, however, is no panacea for those symptoms. It can have significant side effects of its own, including weight gain, liver inflammation, and tremor.



A Drug Tailor-Made for ASD

Oxytocin is a peptide hormone secreted by the pituitary gland. It floods the bloodstreams of mothers giving birth, facilitating uterine contractions and stimulating milk letdown for breast-feeding. Oxytocin also plays a crucial role in so-called affiliative behaviors: It helps initiate the emotional bond between mother and infant, for example, and enhances the social attachments connecting friends and lovers.

In the 1990s, several researchers proposed that abnormalities in the oxytocin system might play a role in ASD, which typically involves poor social skills. Dr. Hollander was the first to study that possibility, in a double-blind, placebo-controlled trial whose results were published in 2003. His oxytocin-related research led directly to a phase 2 clinical trial now evaluating the first drug designed specifically to treat ASD.

"Studying oxytocin made sense to us," Dr. Hollander says. "It had potential for improving the social deficits that are a core symptom of ASD. And it might help correct the E/I imbalance in ASD, since one of its modes of action involves strengthening signals sent by inhibitory neurons."

Dr. Hollander's clinical trials have found that oxytocin significantly reduced repetitive behaviors in people with ASD and made them better aware of social cues in conversation. But administering oxytocin is difficult: The protein must usually be given intravenously or intranasally, since it's broken down in the gut when swallowed. To get around that problem, the Swiss pharmaceutical company Roche designed an oral ASD drug that boosts oxytocin's effectiveness by blocking a chemical competitor called vasopressin.

Oxytocin and vasopressin have a lot in common. The structurally similar peptide hormones are both released by the pituitary gland, and both strengthen social bonds by binding to the same receptors in the brain—but oxytocin is considered more helpful.

> *"Oxytocin had potential for improving the social deficits that are a core symptom of ASD."*
>
> *— Dr. Eric Hollander*

Balovaptan, the drug developed by Roche chemists, prevents vasopressin from binding to a type of vasopressin receptor called V1a. By blocking vasopressin, balovaptan allows oxytocin molecules to bind to those receptors unchallenged—and, it is hoped, will help people with ASD become more socially engaged.

Balovaptan has already been shown to improve social behavior and reduce cognitive impairment in an animal model of ASD and in adult ASD patients. In 2018, the FDA granted balovaptan "breakthrough therapy" status, a process in which the agency speeds its review of drugs that "demonstrate substantial improvement over available therapy" for treating serious conditions.

Dr. Hollander is now leading Einstein's participation in a nationwide clinical trial of balovaptan. This phase 2 (safety and efficacy) trial, called the aV1ation Study, will include 300 high-functioning children and teens with ASD at 30 sites around the country. Participants will take either of two doses of the drug or a placebo for 24 weeks.

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A Marijuana Extract for Autism

More than 100 chemicals known as cannabinoids are found in cannabis plants, including marijuana and hemp. In 1964, researchers identified terrahydrocannabinol (THC) as the cannabinoid responsible for marijuana's "high."

This finding revealed an important signaling system in the brain—one that regulates such physiological and cognitive processes as appetite, stress, mood, memory, social behavior, and pain sensation. THC activates this signaling system by binding directly to receptors in the brain. The human body was later found to produce its own cannabinoids, dubbed "endocannabinoids," which are involved in what is called the "endocannabinoid signaling system."

Recent studies involving animal models suggest that disrupted endocannabinoid signaling may play a role in ASD. For example, in a study published earlier in 2019, Stanford researchers found that the blood plasma of children with ASD contained significantly lower levels of the endocannabinoid anandamide compared with levels in neurotypical children. In keeping with its outside-the-box approach, Dr. Hollander's team is investigating whether cannabinoids might relieve children's ASD symptoms by normalizing endocannabinoid signaling.

The Einstein team has focused on a nonpsychoactive cannabinoid called cannabidivarin (CBDV), whose molecular structure closely resembles that of cannabidiol (CBD)—the popular nonpsychoactive cannabinoid now being sold online and over the counter in tinctures, oils, and lotions for conditions ranging from anger to Alzheimer's. Unlike THC, CBD and CBDV don't seem to bind directly to endocannabinoid receptors, but they nevertheless produce important effects.

> *"This research shows that CBDV has anti-*

inflammatory, immune-modulating, antianxiety, and anticonvulsant properties.

— Dr. Eric Hollander

In two of the few trials that have evaluated CBD in people, New York University (NYU) scientists found that the compound significantly reduced seizure frequency in patients with Lennox-Gastaut syndrome and Dravet syndrome, two rare forms of epilepsy with similarities to ASD. In 2018 the FDA approved Epiodolex, the liquid CBD formulation used in the epilepsy trials, for treating those conditions. CBD's antiseizure properties suggest that CBD and CBDV may both help to correct the E/I imbalance observed in people with ASD.

Preliminary studies have found that CBDV is effective in treating pediatric epilepsy, and animal studies suggest it could be valuable for treating ASD.

"The research shows that CBDV has anti-inflammatory, immune-modulating, antianxiety, and anticonvulsant properties," Dr. Hollander says. "And in one recent study, CBDV improved social behavior in an animal model of Rett syndrome, an autism-related condition. So CBDV appears to be a promising ASD treatment that we need to explore further."

Last year, the Department of Defense awarded researchers at Einstein, Montefiore, and the NYU School of Medicine a $1.3 million grant to study the safety and efficacy of CBDV in children with ASD.

Dr. Hollander is leading the study along with NYU's Orrin Devinsky, M.D., who conducted the CBD epilepsy trials. The hope is that CBDV can help with "protest behavior—the sudden temper tantrums that often plague people with ASD, particularly those with severe symptoms.

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"These tantrums make it hard for families to go to a restaurant, travel on public transportation, or do much of anything outside the home," Dr. Hollander says. "It's a huge burden, one that causes many couples to separate or divorce." Military families who have children with ASD face the same issues, which is why the Department of Defense is supporting the study. "Those families need access to a lot of services, which limits where they can live, which in turn affects military readiness," Dr. Hollander adds.

The Einstein-Montefiore-NYU trial—the first to study CBDV—will enroll 100 children with above-average levels of irritability. Patients will take an oral CBDV solution or a placebo twice a day for 12 weeks, and results are expected in three years. The researchers will use the new Montefiore-Einstein Rigidity Scale—Revised (MERS-R) to assess the participants' social and cognitive functioning before and after treatment.

"We previously had to rely on parents' observations about the children's behavior on scales that were either too specific or not specific enough," Dr. Taylor says. "When we realized we weren't capturing all of their behaviors, we decided we needed a better scale."

MERS-R looks at three domains of behavior: behavioral rigidity (difficulty adjusting to or managing behavior in new, unfamiliar, or unexpected situations); cognitive rigidity (lack of flexible thinking); and protest (behavioral reaction in response to an interruption to the subject's rigidity). "It takes just 20 minutes to administer the MERS-R, which assesses the level, the length, and the severity of each domain and puts a number on it," Dr. Taylor says.

> *Military families who have children with ASD face the same issues, which is why the Department of Defense is supporting the study.*

The findings from the CBDV study could have applications beyond ASD. "The repetitive features of ASD are also common in a variety of other compulsive disorders," Dr. Hollander says. "The goal of our work is to discover ways to target the causes of these conditions, ease the associated symptoms, and improve the quality of life for many, many people."

Recruiting children for the balovaptan and CBDV trials shouldn't be difficult. "Many parents are willing to try anything that might help their children," says Casara Jean Ferretti, M.S., a doctoral student at the Ferkauf Graduate School of Psychology, who helped write the CBDV grant application.

It's an attitude that certainly characterizes Carlos Rodriguez's parents. Carlos didn't benefit from a previous Einstein-Montefiore trial, but that didn't deter his parents from enrolling him in the balovaptan trial. They realize the urgency of finding therapies that will help Carlos and other children with ASD.

"I'll be his advocate to the end of the day," says his mom, Maribel. "I don't want him to feel that he cannot have a life like everyone else. But I do worry about his future. When I try to talk to him about what he's going to do when he gets older, he says, 'I'm not leaving. I'm staying with you.'"

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