DEEP DIVE

Why trials of autism treatments have a placebo problem

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What started as a seed of doubt in Leigh Merryday Porch's mind had, by 2010, become a conviction. Her 18-month-old son, Callum, was delayed in his speech and motor skills. His hearing was perfect, but he often didn't respond when spoken to. Merryday Porch's family has a history of autism, and she finally realized that her son, too, has the condition.

Not one to sit on her hands, she simultaneously enrolled Callum in Florida's early-screening process, found a developmental pediatrician and, as so many parents do, began **looking into alternative therapies**. A school librarian, she soon happened across a book on autism that mentioned the controversial Florida doctor Jeff Bradstreet. Bradstreet was a vocal critic of vaccines and a proponent of unproven alternative autism treatments such as **chelation** therapy.

Merryday Porch was aware that many people said Bradstreet's remedies were nothing but placebos — inert substances that provide temporary relief (or seem to) only because people hope they will. She freely admits she was never terribly interested in science (she majored in English in college) and that she might not have been skeptical enough. But Bradstreet's theories and treatments seemed above board. "You go to these websites and they look very science-y and very authentic," she says. "I wouldn't say I was convinced this was the answer, but I didn't want to regret not looking into it." She wanted to offer her son every chance to thrive. Because Bradstreet's clinic was only a couple of hours' drive away, she took Callum to see him.

Bradstreet espoused the theory that autism is linked to high levels of mercury — an idea that has been discredited but led to widespread mistrust of vaccines. He also said autism is **related to immune function**, an unproven theory that he told Merryday Porch might explain Callum's case. He put Callum through a series of unusual tests — assays for fecal parasites, tests that purportedly measured free radicals in his blood (available only by sending samples to France) and many assessing Callum's immune system — none of which turned up anything. Still, he prescribed a strict gluten-free diet and a host of supplements, including cod liver oil.

For six months, Merryday Porch went along with the therapies. Unlike many of Bradstreet's clients, she wasn't trying to 'cure' Callum's autism, but rather improve a few of his symptoms, such as his lack of language skills. And at first, she was thrilled with the regimen. After taking cod liver oil, Callum, who rarely spoke, began happily naming characters he saw on television. Her expectation — her profound hope — that the treatment might work was buoyed. But even as her child seemed to be getting better, residual skepticism kept her from trying more involved, potentially harmful treatments. Doubts festered in her mind, aggravated by the fact that the same doctor prescribing the supplements was also selling them.

One day during an appointment, when Merryday Porch had to force her panicked son down on a table for yet another blood draw, she finally snapped. "Every instinct in me just told me: 'Just get out of here and don't come back,'" she says. So that's what she did, giving up the pills and the diets for scientifically accepted treatments such as speech therapy. Bradstreet was eventually forced to leave Florida and then investigated by the U.S. Food and Drug Administration (FDA) for selling fraudulent autism therapies, in particular, one treatment — globulin component macrophage-activating factor — related to the tests he ordered for Callum. Soon after, he apparently **took his own life**.

Today, Merryday Porch says Bradstreet's therapies were a waste of time and money, and that all Callum's gains during that time were either in her imagination or the natural course of his development. If anything, she says, the treatments may have been detrimental. She is grateful she never went in for alternative therapies with strong side effects, although she says Callum — now 7 years old and a happy child — has aversions to certain foods thanks to Bradstreet's diets. She runs a popular **autism blog** that often criticizes pseudoscience. Yet she empathizes with parents who go to doctors like Bradstreet. "It's a placebo, but it's a placebo for the parent," she says. "The alternative is so much harder to accept: the idea that you've allowed yourself to be fooled."

Great expectations:

The placebo effect is arguably the most important psychological phenomenon in medicine. It is said to occur when an illness or the symptoms of one improve after the person undergoes a treatment that has no direct biological link to the improvement. But it's more than that: Placebos can have physiological effects, triggering the release of **neurotransmitters** and other brain chemicals, the same way that a prescription drug might. Scientists today look at the placebo effect as not just an odd psychological quirk, but a window into how the brain mediates bodily functions.

The script for most placebo effects runs this way: A doctor, scientist or other authority figure prescribes a treatment that promises some kind of physical or psychological effect. That creates a belief, or 'expectancy,' as psychologists call it, that works in concert with cues from the doctor (a

smile, a hand on the shoulder, a confident demeanor) and thousands of subconscious psychological associations between doctors, medicine and healing. The brain translates that expectation into actual healing or relief from symptoms, as hormones and neurotransmitters, such as dopamine, serotonin, cannabinoids, opioids and even the 'hunger' hormone ghrelin, change the experience of, say, pain, anxiety or depression. In other words, expectation turns belief into reality.

Placebos are not new: Hippocrates, the father of medicine, observed them; Avicenna, a medieval medical pioneer, warned physicians to beware of misleading positive effects when testing new remedies. In this century, placebo effects were written into the rules governing medical treatment. In 1962, the FDA introduced the requirement that a drug candidate must outperform a placebo control in order to be approved. But the mechanism of the placebo effect has remained a mystery; only in the past couple of decades has it come under serious neurological study. Henry Beecher, one of the founders of modern placebo research, famously found in 1955 that an average of **30 percent of people** taking placebos respond to them. In truth, it's more complicated. In trials of people suffering from conditions such as chronic pain, irritable bowel syndrome or depression, between 60 and 70 percent of people in the placebo arm find relief; the number can be just 10 or 15 percent among people with other maladies. For the conditions with especially high placebo-effect rates, it has become increasingly difficult to create new drugs, because even effective drugs cannot outperform the placebo.

For a long time, experts assumed that placebos had little to no role in autism. One of the central features of autism is a diminished ability to process social information. So the conventional wisdom has been that people with autism would have trouble reading a doctor's subtle social cues that can often drive placebo effects — and, therefore, would not respond well to placebo or sham treatments.

In fact, however, trials of autism therapies have been stymied for decades by large placebo responses. The most famous example was in the late 1990s, with the much-anticipated trials of the hormone secretin. Hopes ran high that secretin would be a good therapy for people with autism, but in a 1999 trial of 60 children with autism or pervasive developmental disorder, **it failed to outperform the placebo**. The commonly prescribed antidepressant citalopram **met a similar fate** in 2009. Both drugs seemed effective in early tests until they were compared with a placebo control. In each case, about 30 percent of the participants in the placebo arm improved, which essentially canceled out the power of the drugs being tested. That number is not nearly as high as placebo responses seen in drug trials for pain or depression, but it is higher than expected for a condition that supposedly precludes placebo altogether. Several teams are starting to look more carefully at the placebo effect in people with autism. Their early results paint a fascinating picture of how belief affects not just people with the condition, but also their families.

“Desperation breeds gullibility, and hope can be unsinkable when it comes to one's child.” Leigh Merryday Porch

Hopes and realities:

Research into the placebo effect in autism can be broken down into three rough categories. The first of these is the result of an experimental necessity: Most measurements in a clinical trial rely on parents’ observations. “Parents are exquisitely attuned to very subtle variations in behavior that may not really be apparent to other observers,” says **Adrian Sandler**, medical director of the Olson Huff Center at Mission Children’s Hospital in Asheville, North Carolina. Sandler worked on the first placebo-controlled secretin trials.

In autism studies, the participants themselves generally do not report how they feel; instead, parents or researchers report their observations of the participants. As in Merryday Porch’s case, many parents notice changes after a treatment that don’t exist. This phenomenon is by no means limited to parents of children with autism. A group of scientists from the Menninger Clinic in Houston, Texas, gave sweet drinks to children whose parents described them as sugar-sensitive. Unbeknownst to the parents, the drinks were actually sugar-free, but parents still **rated their children’s behavior** afterward as more hyperactive and erratic than before.

Along these lines, facilitated communication — a popular technique in which children with autism use a keyboard as an assistant guides their hands — has turned out to be a modern-day Ouija board, driven by the **wishful thinking** of the assistants. The placebo effect doesn’t only interfere with observations made by parents and caregivers: Physicians can also easily become persuaded to see improvement in a child.

One wrinkle here is that often the observed progress isn’t a mirage. In any course of treatment, people tend to take medicines when their condition is at its worst, and then attribute the relief they observe to the medicine rather than to the condition’s natural course. Besides, development in all children happens in fits and starts. A well-timed vitamin supplement can seem to be effective when, in reality, the change is due to a natural spurt in development.

The second way placebos play out in autism research is more complicated. Even if a parent is able to suppress the desire to see a positive outcome, she may reveal signs of her excitement. A new therapy can breathe hope and anticipation into a household. Children, being naturally observant of their parents, may respond to this atmosphere by masking symptoms in order to please their parents. This kind of ‘placebo-by-proxy,’ in which children pick up on cues and expectations from their parents, is common throughout pediatric research because, among other reasons, children are highly suggestible.

“Are we seeing things that are simply just relating to a parental placebo effect? Or are parental expectations influencing the child, and then the child’s behavior changes?” asks **Rebecca Jones**, a

neuroscientist at Weill Cornell Medicine in New York. To pin down parents' role in the placebo effect, Jones, along with Weill Cornell clinical psychologist **Catherine Lord**, compared the accuracy of observations made by parents and clinicians with objective, quantitative measures. The results are unpublished, but Jones says they suggest that researchers must take into account the contribution of expectation from all of the parties involved — the trial participants, parents and clinicians.

In fact, parents' opinions seem to predict how a child responds to placebo. For example, multiple studies have found that children whose parents are optimistic about a trial's results at the outset have a **more robust placebo response** than do children of more clear-eyed parents. A 2012 study showed that children prone to tantrums have fewer spells after they drink a flower essence that **supposedly calms children**, but is actually a placebo. The concoction seemed to work, but the researchers found that its success was more closely tied to the expectations of the parents than the observed behavior of the children.

"If the adults expect little, they get little; if they expect a lot, they get a lot," says **Ami Klin**, director of the Marcus Autism Center in Atlanta and a professor at Emory University.

This disconnect between observed reality and biological reality makes it extremely difficult to measure how a treatment is performing in a clinical trial. In other words, expectation constantly muddies the scientific waters. Sometimes, a placebo apparently affects researchers more than it affects the participants: In a 2009 meta-analysis of trials for depression treatments, researchers rated the participants' improvement almost **three times higher** than the participants themselves did. In a similar meta-analysis of irritable bowel syndrome treatments (a favorite topic of study for placebo researchers because of its high placebo rate), the clinicians rated improvement **50 percent higher** than the participants did.

It's difficult enough to separate placebo from drug effects when participants report their own experiences, says **Karin Jensen**, a placebo researcher at the Karolinska Institute in Stockholm, Sweden, but it's nearly impossible when other people are in the mix. The excitement in the media and the autism community over the secretin trials is a perfect example of this phenomenon, she says. "Most of [autism research] is based on subjective ratings," she says. "Expectations were sky high, and so that was transferred to patients via parents and caretakers."

Of course, not all placebo responses are positive, especially when it comes to the wide world of questionable therapies. If a treatment is painful or uncomfortable, and a child is afraid of the therapy, she might change her behavior to mask her condition. Although there's little research into how fear might change the behavior of a child with autism, some in the autism community are convinced that it can play a big role.

Emma Dalmayne, an autism advocate, has the condition, as do five of her six children. She says uncomfortable sham treatments — such as bleaching agents that can damage the digestive system

— can cause a child to pretend to feel better out of fear. The treatments may seem to the child to be a punishment for her autism-related behavior. “Children aren’t stupid,” Dalmayne says. “If you’re a child and you’ve been told you’ve got monsters living in your tummy and your mom wants to flush you with bleach,” she says, “you are going to stop the stimming behavior, the vocalizing and the flapping.”

Misled by this sort of placebo effect, families may waste precious time, energy and money on worthless treatments that, over time, may even be dangerous.

"If the adults expect little, they get little. If they expect a lot, they get a lot.” Ami Klin

True believers:

Research on how people with autism respond to placebos may reveal not only new insights about autism, but how placebos work in a broad range of conditions. Scientists often say that because placebo effects require complex traits such as self-awareness and social cognition, they are likely to be less powerful in people with intellectual disabilities. Results of the few studies that have looked into this dynamic have turned out to be a bit more nuanced, however.

One 2015 meta-analysis of 22 papers by Jensen’s team showed that people with a whole host of conditions characterized by intellectual disabilities — including Down syndrome and the autism-linked **fragile X** and Williams syndromes — experience **objectively measurable placebo responses**. However, the study did find that individuals with higher intelligence quotients experience stronger placebo effects than those with lower ones. And those with dementia experience none.

The 2009 study of citalopram for autism had a similarly informative finding. Overall, the drug did not alleviate **repetitive behaviors** in children, but a more fine-grained analysis revealed an interesting pattern. Children with the most severe symptoms responded significantly less to the placebo than did those with milder symptoms.

Children with autism may not respond as strongly to placebos based on verbal instructions (as in: “Take this pill; it will make you feel better”) as typical children do, though no one has studied that specifically, says **Luana Colloca**, a neuroscientist at the University of Maryland in Baltimore. But there are plenty of other ways a placebo effect might emerge, triggered simply by the act of taking a medication. “Taking a pill is such a strong conditioned stimulus,” Colloca says. “You don’t need to have strong expectations, you don’t need to have strong beliefs; it’s such an automatic response.”

For example, if every time you take a pill, it eases your pain, eventually the pain relief may not depend on what's in the pill, but rather on the act of popping the pill. In the case of pain, the mechanisms by which the brain responds to this repetitive conditioning — by releasing natural opioids — are well documented. In the case of autism, how placebos work is still anyone's guess — but there is some indication that statistical quirks and wishful thinking don't fully explain what scientists are seeing so far, says Sandler. "If you think you are better, you may actually be better. And there's no reason to suppose that that kind of phenomenon might not occur in autism," he says.

It seems unlikely that parents are driving the entirety of these placebo effects — otherwise the responses for the children with mild symptoms should be the same as for those with severe symptoms.

Researchers and parents aren't always seeking to treat autism itself but rather the diverse set of conditions such as anxiety, depression or stomach pain that frequently accompany autism. These conditions are often highly responsive to placebos, and separating out which of them is responding to the treatment is nearly futile. Still, there are steps scientists can take to better understand the placebo effect in autism.

"I would be very interested to see trials in autism where there's both objective measures of [a child's] skills to see if they themselves display placebo effects, and the subjective ratings from parents, clinicians, teachers and caregivers," says Jensen — something Jones and Lord's unpublished research may get at. Enough data like this, Jensen says, and scientists might begin to tease apart where a parent's expectation stops and a participant's begins.

Testing treatments for the behaviors associated with autism is already complicated because of the condition's notorious diversity, says Jones. "When you add on something as complicated as the placebo effect, it almost feels overwhelming in terms of trying to piece out the different components."

Placebos complicate the search for medicines at every level. Drugs are harder to bring to market, ineffective therapies take longer to discredit, and people are led by their false hopes; in the worst cases, crackpot remedies can cause real harm. At the same time, placebos also offer a powerful glimpse into the power of the mind on the body.

Merryday Porch, who has seen both sides of the power of placebo, says she respects how strong its pull can be. "Very few are able to step away," Merryday Porch says of her fellow parents. "Desperation breeds gullibility, and hope can be unsinkable when it comes to one's child. [The experience] taught me much about the power of the mind to see what one wants to see."