VIEWPOINT

Better behavioral tests may save trials of autism treatments

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Connecting matters: Helen Tager-Flusberg links autism science to society.
Illustration by Ivan Canu

The ‘holy grail’ for autism research is treatments that will safely decrease symptom severity, improve everyday functioning and enhance quality of life. In the past decade, we’ve seen a surge in basic neuroscience research that lays the groundwork for drug discoveries. But what are the challenges we face in developing these remedies for autism?

There is no shortage of promising leads. Some of these have even improved social behavior and other symptoms in mouse models of autism. Yet, so far, not one of these drugs has lived up to its promise in people. The number of medications that ease the core symptoms of autism in children or adults is the same as it was 20 years ago: zero.

Part of the problem may be our current approach to drug trials. At their best, these are double-blind, meaning neither the researchers nor the parents know which children are getting the drug rather than a placebo. But they tend to rely on **subjective ratings of improvements in the child’s behavior**.

This subjectivity opens the door to placebo effects. Most published studies (and many unpublished ones) of trials have found significant improvements in children assigned to the treatment group. Unfortunately, children in the placebo group have **also shown gains**, so we can’t conclude that the positive changes result from the drug itself.

Placebo effects are enormously frustrating for everyone involved in a drug trial. In many cases,

both researchers and parents are convinced that a drug worked for some of the children. But if the same improvements are seen in children who received the placebo, the drug is dead in its tracks.

We don't understand what is responsible for this placebo effect. Perhaps parents interact differently with their children because they think a drug is making a difference. Perhaps teachers deliver behavioral interventions more intensely when they know a student is enrolled in a clinical trial of a drug. Perhaps there's a tendency to see positive changes over time, regardless of what a child is receiving. All of these confounds must be explored.

We do have good evidence that behavioral interventions work for many children with autism, especially when provided early in life. These trials are usually not double-blind, so there's no placebo effect. (It's easy to create a fake pill, but impossible to mask specific elements of a behavioral treatment.) They also tend to use more objective measures of children's behavior, such as standardized tests of cognition or language ability.

Yet the data supporting most behavioral interventions are hardly overwhelming. Few are backed by a published randomized controlled trial — the gold standard for teasing out a treatment's true effects. Instead, the literature is steeped in single-case-design studies that provide an initial proof of concept rather than a rigorous evaluation of how well an intervention works.

Scientists also cannot agree on which behavioral measures to use in these trials or even what a good result would look like. Because researchers are not required to specify their outcome measures in this type of trial, they often report only their best outcomes. What's more, it's unclear how results for behavioral interventions delivered by therapists at individual clinics will hold up when **implemented more widely or in the community**.

We have to correct these problems by agreeing on rigorous standards for testing such interventions. And soon, we need to move away from testing medications and behavioral methods in isolation. Even when we have effective drugs, children with autism will still need to learn certain skills and behaviors. Drugs will never replace developmental and educational programs. As a result, we need to bring together researchers involved in testing each type of intervention to design innovative studies that combine the approaches.

Combinations of drug and behavioral therapies are far more effective than drugs alone for psychiatric conditions such as depression, schizophrenia and attention deficit disorder. As we home in on new drug treatments for autism, surely we shouldn't spend years and millions of dollars on costly clinical trials that ignore the lessons of these other fields. The sooner we merge the best of what biology and behavior can offer, the sooner we will achieve our ultimate goal of safe, effective treatments for the full spectrum of autism symptoms.

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