NEWS

Multi-lab study hints at benefits of long-tested autism drug

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The drug arbaclofen eases atypical behaviors in multiple mouse models of an autism-linked genetic condition, according to a new unpublished **study**.

Arbaclofen, which dampens neuronal activity, has been eyed as a potential treatment for **fragile X syndrome**, and a 2012 clinical trial found that it did improve **social behaviors** in people with the condition. But those results did not hold up in a **subsequent trial** in children and adults with the syndrome. The drug's effects in a broader population of autistic people have been **mixed**. Most recently, two small **clinical trials** in autistic children and teenagers did not meet their primary endpoint of improving social function, but they did reveal some improvement on a secondary measure of social function in addition to easing repetitive behaviors and motor difficulties.

In a 2017 study, the drug **improved cognition** in two mouse models of 16p11.2 deletion syndrome — an autism-linked condition caused by loss of a portion of chromosome 16, and eased social problems in one of the models. But the diversity of mouse models and study designs makes it difficult to interpret those results, says **Elizabeth Berry-Kravis**, professor of pediatrics and neurological sciences at Rush University Medical Center in Chicago, Illinois, who worked on the fragile X trials but was not involved in the new study.

Also, journals tend to publish only positive results, which makes it look like "the drug works for everything in the animal model," says Berry-Kravis, "and then reality hits when you try to use it in people."

The researchers in the new study aimed to combat that publishing bias by bringing together a consortium of labs to test arbaclofen in a standardized fashion in three different 16p11.2 mouse models — each harboring a slightly different version of the genetic variant. The results, posted on bioRxiv in May, showed the drug improved cognitive and behavioral issues in the mice.

That was “very encouraging,” says study investigator **Brigitta Gundersen**, senior scientist at the Simons Foundation Autism Research Initiative. “Where there was a phenotype to be rescued — of the phenotypes that we were expecting to rescue — arbaclofen rescued it.” (*Spectrum* is funded by, though editorially independent of, the Simons Foundation Autism Research Initiative.)

In two of the three mouse models, the animals showed impaired performance on a test of their ability to distinguish between new and familiar objects. Treatment with arbaclofen, which was administered through their drinking water, improved that deficit in both models.

Each team also conducted one other behavioral test: either a different memory test, a test of motor function or a fear-conditioning test. The 16p11.2 mice performed unusually on only the motor-function task: They were able to stay on a rotating rod for longer than wildtype mice, and arbaclofen did not change that.

One of the mouse lines also showed atypical behavior patterns when placed in an open field, according to analysis by a fourth lab, which used an unsupervised machine-learning approach called **MoSeq** to parse the animals’ movements. Arbaclofen normalized the model mice’s behavior, the team found.

In people, sedation is the most commonly reported side effect of arbaclofen, according to **past work**. But the drug did not seem to make the mice sleepy or sluggish, based on their tracked movements, and it did not significantly affect other behaviors measured in model or wildtype mice.

> “Where there was a phenotype to be rescued — of the phenotypes that we were expecting to rescue — arbaclofen rescued it.” Brigitta Gundersen

“Bottom line is that there is clearly adequate preclinical proof of concept to justify human trials with arbaclofen, considering its good safety profile,” says **Mark Bear**, professor of neuroscience at the Massachusetts Institute of Technology, who was involved in the trials of arbaclofen for fragile X syndrome but not in the new study.

What might happen in those human trials, however, remains to be seen. The **clinical trial** of arbaclofen in people with 16p11.2 deletion is still recruiting participants and is not expected to end until March 2025. (Clinical Research Associates, an affiliate of the Simons Foundation, owns the patent rights to develop arbaclofen for neurodevelopmental conditions — including autism and fragile X syndrome — and is sponsoring the trial.)

Seeing some level of consistent response across the 16p11.2 mice does seem promising, Gundersen says, particularly in the face of “all of these subtle differences that can cause problems with reproducibility in mouse behavior studies,” such as variability between labs and mouse lines.

Berry-Kravis agrees that the new study's approach is a "good step in the right direction." The findings could help researchers understand "what the drug does and doesn't do," she says, and could aid in selecting the most relevant clinical trial endpoints, for example.

But, as she points out, "it doesn't solve the problem that mice are mice, and people are people."

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