NEWS

Drug improves social deficits in fragile X syndrome

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Normalizing neurons: Treating mouse models of fragile X syndrome (middle) with the drug arbaclofen (right) pares down the number of neuronal projections to normal levels (left).

A drug called arbaclofen improves behavioral problems in people with **fragile X syndrome**, an inherited condition that can lead to mental retardation and autism, according to the results of a clinical trial published today in ***Science Translational Medicine***. A second study published in the same journal showed that the drug restores normal brain function in a mouse model of the disorder[1,2].

The trial of 63 people, led by **Seaside Therapeutics** of Cambridge, Massachusetts, found that the drug, taken for one month, improves measures of social impairment, particularly in those with the biggest deficits.

The drug's success marks a paradigm shift in drug development for neuropsychiatric conditions, several researchers say, showing that scientists can develop drugs that work on the faulty brain mechanisms that underlie the disorders.

"We have our toe in the door of a new way of thinking about how to treat brain disorders,"

says **Allan L. Reiss**, professor of psychiatry and behavioral science at Stanford University, in California, who was not involved in the research. “Historically, the best we’ve been able to do is treat symptoms.”

Arbaclofen is also being tested in clinical trials of adults with autism, but results from these studies are not yet available.

Clear effects:

People with fragile X syndrome lack sufficient amounts of a protein called FMRP, which regulates production of other proteins at the **synapse**, the juncture between brain cells.

Lacking FMRP is like driving a car with only an accelerator and no brakes, says lead investigator on the clinical trial, **Elizabeth Berry-Kravis**, professor of pediatrics, neurological sciences and biochemistry at Rush University Medical Center in Chicago.

Mice missing FMRP show deficits similar to those in people with the syndrome, including hyperactivity, motor coordination problems, and **repetitive** or obsessive behaviors. The second study found that treating the mice with arbaclofen corrects molecular problems, lowering **protein production** at the synapse and restoring density at **dendritic spines**, the tiny neuronal protrusions that transmit electrical signals.

In people, the drug seems to be effective, particularly in alleviating the most severe behavioral problems. Parents noted improvements such as fewer tantrums and an ability to handle transitions and tolerate long car rides. At least one participant was able to have people sing happy birthday to him for the first time.

Berry-Kravis says she treated 14 of the participants and is impressed by how well they tolerated the drug. “The side effects are phenomenally less than almost anything else we can pull out of our pocket for fragile X,” she says. Of those individuals, 10 or 11 are still taking the drug roughly two years after they began, she says.

The results from the placebo-controlled clinical trial must be confirmed in larger trials, which are expected to be completed next year.

The effects of the drug don’t seem to depend on age, suggesting that it will be possible to help both adults and children with the disorder, but that also remains to be confirmed.

Some parents and researchers had been skeptical that treating adults can address neurological problems that emerge early in development. These findings, along with **animal research**, suggest that it is possible to reverse the problems even in adulthood, although that still needs to be confirmed. “We don’t know whether there’s a window that shuts,” says **Aileen M. Healy**, Seaside’s

vice president of research.

Despite its promise, the drug does not seem to lower irritability, its primary goal in the trial. That may be because of a bad choice of endpoints, Berry-Kravis says. The researchers chose irritability because it has previously been used as a measure to win approval from the Food and Drug Administration for autism drugs.

It's difficult to objectively judge when someone with fragile X syndrome improves because there haven't been any drugs to treat its root causes before, says **Randall L. Carpenter**, Seaside's co-founder, president and chief executive officer. Most of the tools used to assess symptoms of autism and fragile X were developed to diagnose the diseases, not to measure the effects of treatments. Seaside is developing **better outcome measures**, Carpenter says.

However, some remain skeptical about the viability of arbaclofen as a widespread treatment.

Despite the benefits reported in the study, the improvement is insufficient to make a substantive difference in these people's lives, notes **Michael Tranfaglia**, a psychiatrist and medical director of the **FRAXA Research Foundation**, an advocacy group that funds research on the disorder, who was not involved in the arbaclofen studies.

"I think there may be some disease-modifying properties, but they may be at a dose that will be ten times what people can tolerate," Tranfaglia says, adding that he hopes to be proven wrong. "I'm anxiously awaiting the results of the [larger] trial."

Berry-Kravis says some patients did tolerate somewhat higher doses, and some of those on the highest doses showed the best response. Subsequent clinical trials are using a maximum dose that is 25 percent higher than the dosage used in this study.

In June, Seaside announced a deal with pharmaceutical giant Roche to collaborate on developing a fragile X drug with a different mechanism.

References:

1: Berry-Kravis E.M. *et al. Sci. Transl. Med.* **4**, 152ra127(2012) **Abstract**

2: Henderson C. *et al. Sci. Transl. Med.* **4**, 152ra128 (2012) **Abstract**