NEWS

In trials, repurposed drug shows promise for autism

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A drug used to treat excessive swelling seems to ease autism features in some children on the spectrum, according to results from a trial in France[1]. But there are concerns about the drug's side effects, as well as possible placebo effects in the trial.

Clinicians prescribe the drug, called bumetanide, to relieve fluid retention after heart failure and in people with liver or kidney disease. The drug is also used to lower blood pressure. In the brain, it affects a chemical messenger, gamma-aminobutyric acid (GABA), thought to be important in autism.

The study is the largest to investigate the drug's effects on people with autism. In 2010, the same team reported that five children showed modest improvements on tests of autism severity after taking bumetanide for three months[2]. They reported **similar gains** in a 2013 study of 27 children with autism.

In the new work, published 14 March in *Translational Psychiatry*, the researchers tracked the effects of bumetanide in 88 children taking three different doses of the drug or a placebo. They found that bumetanide appears to decrease autism severity in a dose-dependent manner.

"Bumetanide does succeed in reducing severity of autism in children," says lead researcher **Yehezkel Ben-Ari**, who is president and co-founder of **Neurochlore**, the French biotech firm that holds the patent for bumetanide as an autism treatment. Children who began taking the drug in the 2013 trial continue to use it, Ben-Ari says, and their parents report that the children "are more present."

The new results drew praise from autism researchers — with some important caveats.

"This is another exciting chapter in a series of pilot studies on bumetanide," says **Jeremy Veenstra-VanderWeele**, associate professor of psychiatry at Columbia University.

But he and others note that the trials may have been influenced by a strong placebo effect. Because the drug is a diuretic — meaning it causes excessive urination — parents might have figured out whether their child was receiving the drug or a placebo, Veenstra-VanderWeele says. The researchers took pains to make sure that the trial investigators did not know which children were in the drug arm versus the placebo arm. But "it is particularly challenging to blind families to treatment assignment when the medication being studied is a diuretic," Veenstra-VanderWeele says.

The drug would need to be taken under close medical supervision, adds **John Jay Gargus**, director of the Center for Autism Research and Translation at the University of California, Irvine, who was not involved in the work. "Nothing makes you pee like bumetanide," Gargus says. "I'm kind of nervous that people will rush out and give their kid bumetanide — and then kids will die."

Moderate gains:

The trial included 88 children with autism ranging from 2 to 18 years of age. One group took a placebo syrup, and the others received either 0.5, 1 or 2 milligrams of bumetanide twice daily for

three months.

Of the initial enrollees, 15 dropped out, most of them because of side effects such as severe dehydration. Two of the children were so dehydrated that their parents had to take them to the emergency room. (The researchers dropped two children from the placebo group for reasons unrelated to side effects.)

Of the 66 children who took bumetanide, 23 showed an improvement of more than 6 points on the Childhood Autism Rating Scale (CARS); only 1 of the 22 children on the placebo showed similar gains. (Clinicians administer CARS to rate features relevant to autism, such as the ability to communicate with others or to imitate them. Scores range from 15 to 60 points; a score of more than 30 signals autism.)

Children taking the drug also improved more on the Social Responsiveness Scale, a parent questionnaire that measures social ability, than did the placebo group.

The children taking the highest dose of bumetanide, 2 milligrams, showed the most improvement — an average of 5.35 points on CARS. This dose also led to the most severe side effects: Of the 22 children in this group, 9 dropped out of the study.

This might skew the results, because parents who don't see any improvement are the most likely to drop out of the study, says Gargus.

Ben-Ari says he plans to use the 1 milligram dose in future studies.

Keeping balance:

Ben-Ari's team first considered bumetanide as a therapy for autism because of its ability to modulate the effects of GABA. This chemical messenger dampens neuronal responses, but early in development, its effects are the reverse: It excites neuronal signals.

Ben-Ari speculated that rather than make this developmental switch from excitatory to inhibitory, GABA remains excitatory in children with autism.

Some studies suggest that children with autism have **especially excitable brains**. And in one small study, sedatives that enhance GABA activity increased aggression in children with autism[3]. The strongest evidence came in 2014 when Ben-Ari's team discovered that GABA remains excitatory unusually late in development in **two autism mouse models**.

Bumetanide partially blocks channels that admit chloride ions into neurons. Because GABA opens chloride channels, bumetanide switches the cell's response to GABA from excitatory to inhibitory.

A study published 23 February in *Annals of Neurology* supports this theory. Researchers found that severe seizures in rats switch GABA's function from inhibitory to excitatory. This switch rewires the brain, making the rats even more seizure-prone. Giving bumetanide after a seizure reverses the switch and decreases the frequency of seizures[4].

"We show that GABA can be linked to structural changes in the brain. One could imagine maybe something similar might be happening in children with autism," says **Claudio Rivera**, lead investigator on the study and research director at the University of Helsinki in Finland.

Ben-Ari and his team plan to begin recruiting 370 participants from five European countries for a new bumetanide trial at the end of this year. If the study confirms their findings, the drug could be on the market for autism in Europe in a few years, Ben-Ari says. Researchers will have to conduct a separate U.S. trial of the drug to gain approval from the U.S. Food and Drug Administration.

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