

Q&A

Diabetes drug delivers multiple benefits for people with fragile X syndrome

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Researcher Randi Hagerman is a big proponent of metformin — a diabetes drug that helps people manage their weight. In fact, Hagerman takes the drug herself as a preventive measure against cancer.

Metformin has also unexpectedly shown promise for **improving cognition** in people with **fragile X syndrome**, a **leading genetic cause of autism** characterized by severe intellectual disability.

Hagerman tells *Spectrum* how the drug might work and why she is excited about the results of a three-year clinical trial that aims to quantify metformin's effect in people with the syndrome.

***Spectrum*: What treatment options are currently available for fragile X syndrome?**

Randi Hagerman: There are no treatments approved [by the U.S. Food and Drug Administration (FDA)] to treat the syndrome yet, but a host of medications work pretty well, including some stimulants and antidepressants. We also prescribe aripiprazole — [an atypical antipsychotic] — melatonin, antioxidants and different kinds of supplements.

But many doctors won't use any medications that are not FDA-approved.

S: Metformin is not yet approved to treat fragile X. How did you first become interested in it?

RH: A study published in 2017 **linked impaired insulin signaling** in the brain to cognitive and social deficits in a fruit fly model of fragile X, and the flies improved on metformin. A second paper that year showed that **metformin reverses abnormalities** in a mouse model of the syndrome, including the number of branches the mice's neurons form. It also improved seizures and hyperactivity in the mice — issues we also see in people with fragile X.

I began prescribing metformin to people with fragile X syndrome to help curb overeating. Many of the people I treat are overweight because of this habit — it's one of the symptoms of a subtype of fragile X called the Prader-Willi phenotype, not to be confused with **Prader-Willi syndrome**.

I was surprised when the families of these individuals told me they could talk better and carry out conversations, where they couldn't before. That really gave us impetus to conduct a controlled clinical trial.

S: How does the drug boost cognitive abilities in people with fragile X?

RH: The condition is caused by mutations in the FMR1 gene. FMR1 codes for a protein called FMRP, which regulates the expression of hundreds of other genes. If FMRP is disrupted, protein production may increase in the brain and elsewhere in the body because FMRP's inhibitory effect is missing.

Metformin dampens several pathways that are overactive in fragile X syndrome, and rescues some physical and language abilities.

S: You're conducting a clinical trial of metformin for people with fragile X. What is the status of that trial?

RH: We are in our second year of the study and are enrolling people in three locations: the University of Alberta in Edmonton, Canada; the Sainte-Justine Hospital in Montreal; and the MIND Institute at the University of California, Davis.

Our study looks at people with fragile X syndrome aged 6 to 25. Participants take either metformin or placebo for four months, and we assess them using a whole battery of cognitive tests.

We have more boys than girls enrolled because our intelligence quotient (IQ) cutoff is 79, and many girls with fragile X have an IQ above 80.

We have more than 20 people enrolled at the MIND Institute and expect to get another 20 this year; the other two locations are just starting to enroll now. We expect to register 60 at each site per year over three years — enough to allow us to see changes in language and cognitive performance.

S: How are you measuring the cognitive effects of the drug?

RH: We are using an extensive language assessment and the **NIH Toolbox**, which has a whole battery of measurable neurocognitive outcomes. The scales have been adjusted to work well in individuals with cognitive disability. We are also using the **Tobii eye tracker**, which provides a quantitative measure of how the brain processes eye contact — something that people with fragile X often have trouble with.

These toolboxes are useful because behavioral checklists can be skewed if they're answered by caregivers; if a parent believes a medication will cure her child, her answers can be biased.

S: Does the drug have any side effects?

RH: Persistent loose stool is a possibility. But most of the people I see don't have any diarrhea. Starting the medication slowly and increasing the dose gradually helps avoid this problem.

S: What effect does the drug seem to have in people with fragile X?

RH: It's not a cure-all, but we do see some positive changes. It doesn't resolve intellectual disability, but we have seen IQ improvements of up to 10 points in two boys who have been treated with metformin. We are very excited about that.

Individuals on metformin tend to start eating less, and often lose weight as a result. I could kick myself, because metformin has been approved to treat obesity for many years, but I never thought

to use it in fragile X syndrome. Oftentimes children with fragile X syndrome have so many problems that you aren't thinking about obesity as the top priority.

We've also seen a gradual effect on language, which we can detect after two to three months. Sometimes there are improvements in other behaviors too; I've seen mood-stabilizing effects. Many people with fragile X syndrome have issues with aggression, and it's possible these could be moderated with metformin too.

S: When do you expect to have final results from the trial?

RH: We have at least two more years of collecting data, and then we will analyze it. In the meantime, I'm prescribing metformin to some people with fragile X syndrome who visit my clinic if they cannot participate in our study.

S: If metformin controls weight and boosts language learning, why isn't everyone taking it?

RH: Well, I am! When I started reading and found out that it can also help prevent some forms of cancer, including breast cancer, I decided to start taking it myself. I even lost some weight. I don't know why others don't take it if they are overweight or concerned about their cancer risk. Ask your doctor.