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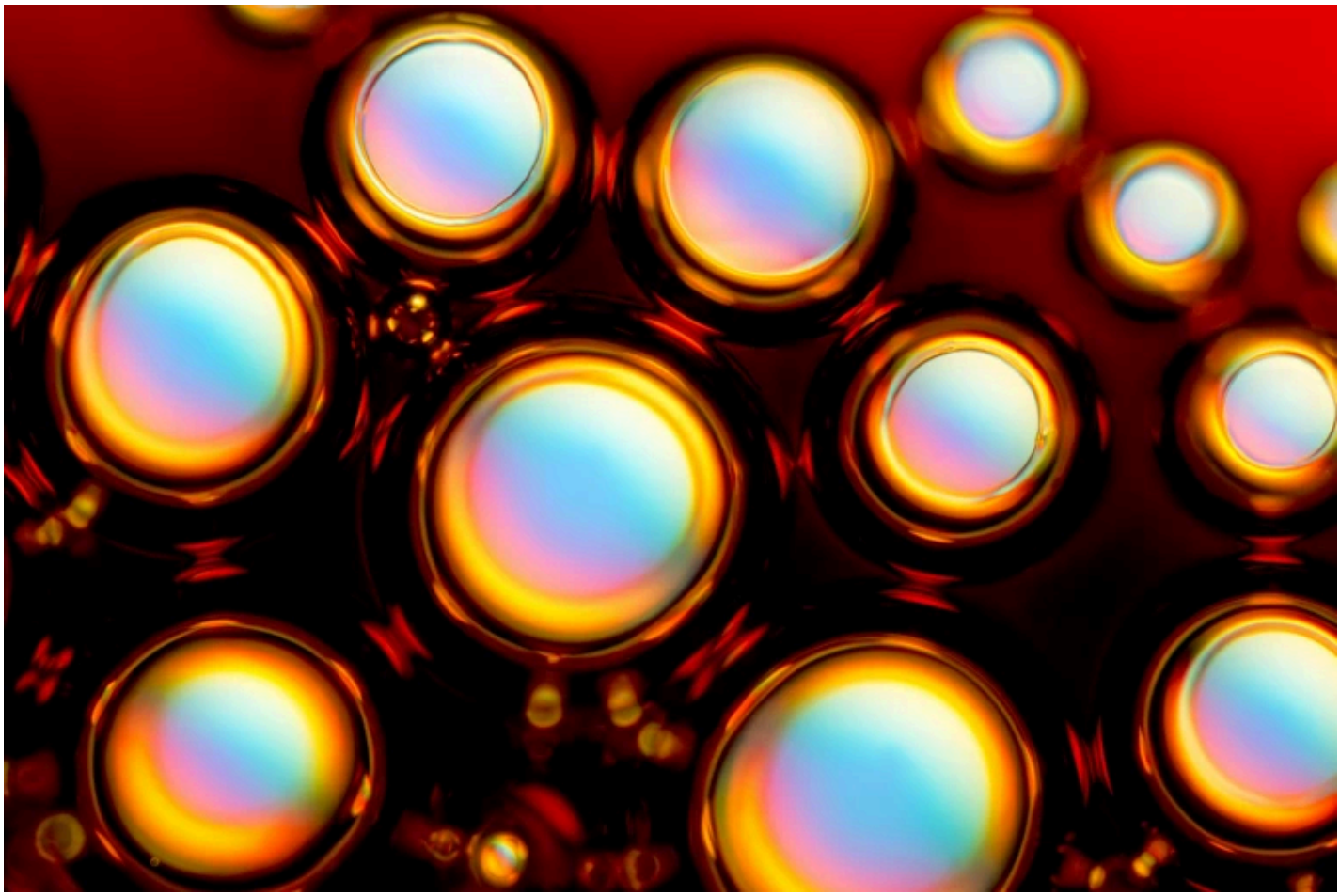
Trump team backs an unproven drug for autism — but does it work?

Leucovorin would be available only to a minority of autistic people, and has not been tested for safety or effectiveness in a large trial. Some researchers are worried.

By Heidi Ledford



Globes of folinic acid, also called leucovorin, which Trump team officials have promoted as an intervention for autism. Credit: Alfred Pasieka/Science Photo Library

According to Martin Makary, head of the US Food and Drug Administration (FDA), the drug leucovorin will help "hundreds of thousands of kids" with autism. But a day after Makary praised leucovorin's powers at a White House event, some specialists are warning that the science to warrant Makary's enthusiasm is far from solid.

Those researchers say that the drug's efficacy has not been established, that scientists don't know how much of the drug to give or how people should take it, and that safety data in children are lacking. According to the FDA's current plans, leucovorin will be available to only a minority of autistic people.

All of this has led to widespread confusion, say clinicians, who also worry about the expectations created by Makary and other officials in the administration of US president Donald Trump.

"I've heard from a lot of families," says psychologist Catherine Lord at the University of California, Los Angeles. "The major thing they say is, 'What is this? What do we do?'"

"I don't want to get everyone's hopes up that this is a magic cure," says Rebecca Schmidt, a molecular epidemiologist at the University of California, Davis. "It's not for everybody."

Vitamin in the spotlight

At an announcement on 22 September, Makary announced the upcoming approval of leucovorin, a form of the vitamin folate, by saying it would "open the door to the first FDA-recognized treatment pathway for autism". People with low levels of folate in the protective fluid surrounding the brain and spine can sometimes exhibit traits associated with autism, including challenges in social communication. This condition, called cerebral folate deficiency, could be due to rogue antibodies that attack the body's own proteins – in this case, proteins that ensure import of folate into the brain.

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There have been clinical trials of leucovorin, also called folinic acid, in autism, but the studies to date have been small. For example, one recent clinical trial enrolled about 80 children aged 2 to 10, and provided folinic acid supplements to about half of the participants[1]. Neither the participants nor their physicians knew who received the supplement and who received a placebo. Participants who received the supplement reported greater improvements in social interactions and language skills than those who received the placebo.

After the trial was published, some researchers subsequently raised concerns that the assessment of those improvements was subjective, and that the study was too small to detect subtle differences in response[2].

Call for bigger trials

But size is not the only thing that matters in clinical trials, says Dan Rossignol, a family physician in Aliso Viejo, California, who has studied the data on leucovorin and sometimes prescribes it to autistic children. The effect of leucovorin in the trials has been large enough to be apparent even with small numbers of participants, he says. Specifically, Rossignol points to an early leucovorin clinical study, in which only 48 children participated but some experienced marked improvements in a standardized assessment of speech[3].

"But it would be great if more studies were done with more kids," he says. "Then we could tease out which kids respond better." Typically, studies submitted for FDA approval of a drug for autism might have data from hundreds of children, he says, but it has been difficult to raise the money for bigger trials. Rossignol says that he and a colleague have been in discussions with US President Donald Trump's administration to make the case for leucovorin.

On Monday, the Trump administration said the US National Institutes of Health plans to monitor the effects of the FDA's anticipated approval and to study possible broader benefits of leucovorin in autistic people. No details have been released as to how such studies will be designed.

Not a magic bullet

Regardless of the therapy's efficacy, it will not be a panacea. The FDA's proposed approval, which has not yet been finalized, would apply only to people with low levels of folate in the fluid surrounding the brain and spinal cord. That represents about 7–30% of autistic people, depending on how folate levels are measured, says Alycia Halladay, chief science officer of the Autism Science Foundation in New York City. "Families are in the Facebook groups saying, 'We can get a prescription now'," she says. "And that's not what's going to happen."

Autism is complex and thought to be caused by a wide range of factors. No single therapy is likely to apply to all autistic people. “If anyone tells you they have found a magic bullet cure for autism, doubt them,” says Halladay. “There is not going to be one cause and one singular treatment.”

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The lack of data from large trials means that doctors will have little to go on when determining what dose to prescribe, or how long children should take leucovorin before deciding if it is or is not working, says Halladay. “We hope there’s eventually going to be guidance,” she says. Rossignol says that most of the clinical studies of leucovorin in autistic children have used the same dose, which could provide a starting point for physicians.

Leucovorin has long been used to alleviate some side effects of chemotherapy and immune-suppressing treatments and appears to be safe in that context. But there is scant data to confirm that it is safe for autistic children, says Schmidt. “I don’t know of any evidence showing real harm,” she says. “But there’s also just not a lot of evidence yet in this population.”

Schmidt is particularly concerned that pregnant people might start taking leucovorin. “Less is known about appropriate doses and things like that during pregnancy,” she says.

False positives

Meanwhile, some families with autism have been clamouring for leucovorin for years, sometimes shopping around for physicians who will prescribe it to them despite the lack of FDA approval as an autism medication. Rossignol says people have come from 80 countries to visit his clinic and that his two children with autism have benefited from leucovorin treatment.

Lord says that she knows neurologists who have agreed to prescribe the drug despite misgivings about a lack of data, because at least then they know that they can monitor the drug's safety in their patients. And Lord remembers when results from small clinical trials of other autism interventions in years past energized the autism community, only to yield disappointment when large studies proved the results to be false positives.

"It's very easy to get false positive findings in autism research," says James Cusack, chief executive of Autistica, a UK autism research and campaigning charity in London, who is autistic. "The threshold for demonstrating something is efficacious is very, very high in autism."

Not everyone with autism is seeking treatment. Some groups and autistic people would like there to be treatments, Cusack says, and "their voice is important in this whole discussion." But many people find the narrative and fear around autism that is being generated by the Trump administration to be stigmatizing and negative, he says: "The whole thing is a distraction, a waste of time and resource and effort."

Cusack says the urgent goal should be to recognise the inequalities that autistic people experience, and find ways to ensure autistic people get healthcare, mental health assistance and employment support.

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With additional reporting by Helen Pearson

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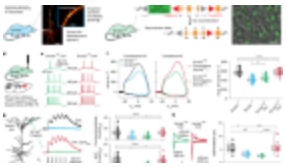

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