VIEWPOINT

Why serotonin medications may yet help children with autism

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A class of medications used to treat depression, anxiety and obsessive-compulsive disorder seems to ease compulsive behaviors in adults with autism. These medications, called serotonin reuptake inhibitors (SRIs, also known as SSRIs), work by increasing the available levels of the neurotransmitter serotonin in the brain and include fluoxetine (Prozac) and citalopram (Celexa).

But three prominent studies — two published within the past year — have reported that these medications do not appear to alleviate **repetitive behaviors** in children with autism[1,2,3].

How are we to interpret these results? Do the studies indicate that this entire class of medications is useless for treating autism? Or do they instead reveal problems with the way the medications were tested?

With so few autism treatments backed by **solid evidence**, we must be meticulous in our examination of these 'negative' studies — and avoid hastily dismissing SRIs' potential for treating autism.

There are three main hypotheses about why SRIs could be used to treat autism. First of all, we know that children with autism show differences in the **serotonin system** compared with their neurotypical peers. (For example, some children with autism have high blood levels of the chemical.) We also know from animal studies that the serotonin system is important for **social reward** and behavioral flexibility[4].

It is logical, therefore, to wonder whether serotonin drugs might be effective for treating autism's core traits.

SRIs are also helpful in children and adults who have conditions that share traits with autism, such as **obsessive-compulsive disorder** (OCD). Like many other conditions that are defined by mental

state or behavior, OCD is treated based on its symptoms; so why not autism, too?

One 2012 autism study, for instance, borrowed its methodology from trials that showed that SRIs are beneficial for people with OCD. The 12-week trial showed that fluoxetine significantly improves compulsive behavior in adults with autism[5]. The researchers gave the participants doses similar to those used in OCD studies, and rather than define an autism-specific outcome measure, they applied the same primary measure used in OCD, modified to focus only on compulsions.

Puzzling questions:

If an SRI works for compulsive behavior in adults with autism, why did three trials in children fail? It is difficult to know for certain, but there are some likely explanations.

First and foremost, none of the three trials focused exclusively on compulsive behavior. Instead, the researchers used an outcome measure that lumped all **repetitive behavior** together, including repetitive play, **hand flapping** and echolalia (repetition of speech). The measure is statistically robust and was developed and tested in the autism population[6]. But it does not map well onto the experience of autistic people, their caregivers and clinicians. There is also substantial clinical and genetic data indicating that preferred interests, compulsions and stereotypies are actually quite different from one another.

There are other reasons these studies may have failed.

Perhaps most vexing, the researchers tested less than half the dosage typically given to children and adolescents with OCD. Even at these lower doses, some of the participants — including many taking the placebo — showed increased energy, disinhibition and hyperactivity.

Remarkably, in the one study of citalopram, children with less severe distress related to their repetitive behavior showed a greater response to placebo than to citalopram. This finding indirectly suggests that for these children, side effects outweigh any potential benefits[7].

The most recent study, a 14-week trial of fluoxetine published in October, had a high dropout rate: 36 percent[1]. Still, the primary analysis showed that children who took the drug improved more than those taking placebo.

If the researchers had stopped there, the trial would have been reported as positive. However, a secondary analysis found that the placebo group had higher repetitive behavior and social impairments at baseline. Once these and other factors were included in the analysis, the greater response in the children taking fluoxetine could no longer be confidently separated from random variation in behavior.

Cautious steps:

So, what have we learned from these studies?

It is possible that children and adolescents with autism and compulsive behavior don't tolerate SRIs as well as autistic adults do, but it is unclear whether this would limit the dose that could be given to them. But we can at least reasonably conclude that low doses of SRIs do not benefit repetitive behaviors in everyone with autism.

We should still absolutely consider SRIs as a treatment option for autistic adults who have distressing compulsive behaviors. In most cases, these behaviors will merit a diagnosis of co-occurring OCD. We should also consider cognitive-behavioral psychotherapy approaches that are effective in OCD, even in the absence of clear evidence that they are effective in those with autism.

In children with autism, based on the dearth of autism-specific evidence, we should prioritize behavioral approaches and consider prescribing an SRI only if the children also clearly have OCD. We should adopt a similar approach for other conditions that respond to SRIs in the general population — including **depression** and **anxiety**, which commonly co-occur with autism.

Above all, we must wait for studies that specifically test the effectiveness of SRIs in treating compulsive behaviors in children with autism.

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