NEWS

Going on Trial: Serotonin drug; psilocybin phase 2; placebo response data

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Welcome to the April edition of Going on Trial, a monthly newsletter covering clinical trials and drug development for autism and related conditions. In this issue, we're talking about a serotonin agonist's path to trial for autism, debate around a trial of psilocybin for fragile X syndrome and an analysis of placebo responses in a clinical trial of the vasopressin blocker balovaptan.

Feel free to email me at **peter@spectrumnews.org** with feedback on how this newsletter can better serve your needs as a researcher, and send me any tips you think readers should know about. In fact, this month's story on psilocybin was prompted by several readers who responded to the **first issue** of Going on Trial.

Serotonin strategy:

Researchers are recruiting autistic adults and teenagers for a **phase 2 trial** of an experimental drug that binds to and activates the serotonin 1B receptor. The drug, called ML-004 and developed by San Francisco, California-based Maplight Therapeutics, belongs to a class of compounds called triptans, which are **prescribed for migraines** and have minimal reported side effects.

This trial is based on more than a decade of research on the mechanisms underlying the rewarding aspects of social interaction, says Maplight co-founder and board member **Robert Malenka**, professor of psychiatry and behavioral sciences at Stanford University in California. "Why do most of us like to go out and have a beer with friends?" he asks. "It's because it's fun. It's usually more fun to hang out with friends than to have a beer by yourself."

The process of learning that social interactions are rewarding calls for **serotonin release** in the nucleus accumbens, a 2013 mouse study in Malenka's lab showed. Blocking or triggering that release **stifles or fosters social behavior**, respectively, the team found in a 2018 study involving an autism-related mouse model.

The drug 3,4-methylenedioxymethamphetamine (MDMA), which promotes serotonin release, and an experimental serotonin 1B agonist called CP-94,253 each **reversed sociability deficits** in six autism mouse models, Malenka and his collaborators showed three years later, convincing them that it was worthwhile to test whether such a drug could help autistic people, he says.

The team opted to use ML-004 in the trial because its active ingredient has a similar action to CP-94,253 and has a history of safe use in people.

“This is an incredibly logical and yet elegant line of work that led to this point,” says **Jeremy Veenstra-VanderWeele**, professor of developmental neuropsychiatry at Columbia University, who did not work on the drug’s development but is involved with one of the trial sites. “I wouldn’t expect it to work in everyone, but it may be helpful for autistic people who don’t find it rewarding to interact with other people — or those who don’t feel connected or engaged with others.”

The trial’s primary endpoint is participants’ change in score on a test of social communication. Overall clinical improvement and improvement on a test of irritability are among the trial’s 12 secondary targets.

Based on the results and conversations with the U.S. Food and Drug Administration (FDA), Maplight plans to decide whether a phase 3 trial should target sociability or irritability, says **Christopher Kroeger**, the company’s chief executive officer. The only FDA-approved drugs for autism, risperidone and aripiprazole, already treat irritability, offering a road map, he says, but “the regulatory pathway and approval endpoints for sociability are less well-defined.”

The company also plans to use eye-tracking software to see if ML-004 increases participants’ focus on social interactions instead of objects in videos. “We’d need to work with the FDA to get that endpoint approved, but I think it’s an interesting objective measure of sociability,” Kroeger says.

Regardless of precedent, and even if it is not a simple path forward, eye-tracking software is a logical tool for monitoring improvements in social function, says **Edwin Cook**, professor of psychiatry at the University of Illinois at Chicago, who is not involved in the trial. “The FDA will understand the importance of this endpoint in autism.” And with a dozen secondary endpoints, perhaps a better one will emerge, he adds.

Drugs targeting serotonin have a mixed history in autism research. Several trials of selective serotonin reuptake inhibitors (SSRIs), which gradually increase serotonin levels in synapses, do not alleviate repetitive behaviors in children, but they do seem to **help autistic adults** with compulsive behaviors, so some researchers, including Veenstra-VanderWeele, maintain that differently designed trials could show benefits for certain people.

Microdose therapy:

“A small clinical trial on the use of psilocybin microdoses to treat fragile X syndrome, sponsored by the Canadian biotech Nova Mentis Life Science, began **recruiting participants in Canada last week**. The move comes on the heels of a **study** on fragile X model rats, funded by the company and published in December, that suggested the experimental treatment is safe and could help alleviate cognitive impairment,” I write in *Spectrum* this month.

"Nova Mentis submitted the rat study results, along with drug manufacturing data, to Health Canada, and because psilocybin has been found to be safe **at much higher doses** than what Nova Mentis plans to use, the company was cleared to **move forward** with a phase 2A trial. The trial will be conducted open label — meaning that all participants will receive the drug, with no placebo control."

“But multiple experts in the field of fragile X treatment and psychedelics research point out that a single rat study does not justify moving on to human trials. It would be “beneficial to see any animal behavioral work in fragile X knockout species replicated at a second lab,” says **Craig Erickson**, associate professor of psychiatry at Cincinnati Children’s Hospital Medical Center in Ohio, because of the difficulty of reproducing behavioral findings in fragile X model mice."

"These doubts around the scientific backdrop for the 2A trial are compounded by the fact that Nova Mentis is running out of money and may live or die by the trial’s results."

Read more in “**Company on brink takes psilocybin to trial for fragile X syndrome**.”

Drug samples:

- The anti-seizure properties of cannabidiol (CBD) come from its ability to halt a **runaway signaling imbalance**, according to a February study on mouse and rat models of epilepsy. Specifically, CBD blocks the action of a molecule that promotes excitation on the signal-sending side of synapses and lowers inhibition on the signal-receiving side.
- The drug giant Novartis has ended its partnership with California-based Sangamo Therapeutics to develop three therapies for undisclosed neurodevelopmental conditions using Sangamo’s zinc-finger technology to fine-tune gene expression, according to a March **filing** with the U.S. Securities and Exchange Commission. Pharma heavyweight Biogen also abandoned its **collaboration with Sangamo** to develop zinc-finger drugs for neurological conditions, including Alzheimer’s disease and Parkinson’s disease. The Novartis collaboration is set to end on 11 June, and the Biogen one on 15 June.
- A phase 2b trial of an experimental drug for irritability in autistic children aged 13 to 17 **has expanded to include** children as young as 5. The drug, developed by Massachusetts-based Axial Therapeutics, blocks a gut molecule linked to brain connectivity issues in mice, *Spectrum* previously reported.
- Intranasal oxytocin reduced autistic children’s functional connectivity between the amygdala and the orbitofrontal cortex, according to **unpublished results** from a double-

blind placebo-controlled trial posted on medRxiv this month. This effect was linked to improved regulation of the autonomic nervous system, especially in participants with higher oxytocin receptor expression.

- Autistic children with depression or attention-deficit/hyperactivity disorder have greater placebo responses than those with autism alone in clinical trials of balovaptan, which blocks the vasopressin 1A receptor, according to an April **study** in *Neuropsychopharmacology*. Balovaptan has **failed to show benefits** in clinical trials for children and adults with autism, *Spectrum* previously reported.

That's all for April. Be sure to **subscribe** so you can receive this newsletter in your inbox every month.

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