NEWS

Going on Trial: Epidiolex for autism; arbaclofen tests; pain monitoring

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Welcome to the May issue of Going on Trial, a monthly newsletter covering clinical trials and drug development for autism and related conditions. This month we're talking about the preliminary findings from a clinical trial of the cannabis-derived drug Epidiolex for autism, the results of two new arbaclofen trials and a trial assessing pain in nonspeaking people.

Epidiolex for autism:

Epidiolex does not ease severe behavior problems in boys with autism, according to preliminary analyses of a **phase 2/3 trial**, says lead investigator **Doris Trauner**, distinguished professor of neurosciences and pediatrics at the University of California, San Diego. Epidiolex — a purified liquid extract of cannabidiol (CBD), which is minimally psychoactive — is already **approved for treating seizures** in people with the autism-linked conditions Dravet syndrome and Lennox-Gastaut syndrome.

In the new study, Trauner and her colleagues randomly assigned 30 autistic boys aged 7 to 14 with severe behavior issues to take Epidiolex or a placebo orally twice a day for eight weeks. The dosage was ramped up during the first three weeks, leveling out at 20 milligrams per kilogram of body weight per day. For another eight weeks, the boys in the placebo group took Epidiolex and vice versa.

The trial had three primary endpoints, which were gauged at the end of both eight-week treatment periods: scores on a standardized parent-report measure of repetitive behaviors, scores on a parent-report measure of problem behaviors, and scores on the Autism Diagnostic Observation Scale, a gold-standard assessment of autism-related behaviors, conducted by clinicians. Neither the parents nor the clinicians knew which drug each child was taking.

Only repetitive behaviors improved significantly more with Epidiolex versus placebo, Trauner says.

Clinicians reported improvements on the Clinical Global Impression Scale, which assesses a person's response to a treatment, in 20 of the 30 participants taking Epidiolex versus placebo, Trauner says. The scale was used as part of participants' clinical assessments but not as a trial outcome measure, "although it clearly should have been," she says. It's possible that the primary outcome measures used in this study were not the best ones for capturing the treatment's effects, she adds.

Trauner says her team still needs to finish analyzing the data, so these results are not set in stone. They also collected MRI and electroencephalography data, which could help show the brain activity differences between responders and non-responders, she says.

Arbaclofen's mixed results:

"Autistic children and teenagers who took the investigational drug arbaclofen fared no better than controls on a rating of social skills, but they showed significant improvements in atypical behavior and other measures, according to the results of two clinical trials presented [5 May] at the 2023 International Society for Autism Research annual meeting in Stockholm, Sweden," **Giorgia Guglielmi** writes in *Spectrum* this month.

"Mouse studies from the past decade have suggested that arbaclofen **eases traits related to autism and other conditions**, but **results in people** have been mixed. (Clinical Research Associates, an affiliate of the Simons Foundation, *Spectrum*'s parent organization, holds the patent rights to develop the drug for autism, **fragile X syndrome** and other neurodevelopmental conditions.)

"One of the new trials included 82 autistic children and teenagers in Canada aged 5 to 17, and the other included 122 autistic people across Europe of the same age range. At the start of both trials, participants were randomly assigned to take increasing doses (up to 20 milligrams) of arbaclofen or a placebo three times per day for 16 weeks."

Read more in "**Trials of arbaclofen for autism yield mixed results**."

From the heart:

A device to **detect pain and discomfort** in nonspeaking people with autism is being tested in a clinical trial. The tool is based on changes in a person's heart rate, and the trial is also collecting data on inflammatory cytokines as markers of chronic or longer-term pain. I spoke with trial investigator **Emilie Smith-Meyer Kildal**, a Ph.D. candidate in clinical medicine at the University of Oslo in Norway, about this tool and the ongoing trial.

This interview has been edited for length and clarity.

***Spectrum*: How did this study come to be?**

Emilie Smith-Meyer Kildal: It started at the Department of Neurohabilitation at Oslo University Hospital, a department for people with epilepsy, intellectual disability and often autism with co-occurring difficulties. A patient there, whom I'll call Emma, came to our clinic because her caregivers were worried that something was wrong. She couldn't move her hands, she couldn't speak, and she could barely move her eyes. She could make some sounds, but none that her caregivers could make any sense of. We asked them, "How do you know that Emma is in pain?" They said, "We know something is wrong when she is drenched in sweat." We thought to ourselves, then she must have been in intense pain for a long time. Surely, there must be some way to detect this sooner. That was the beginning of the project.

S: How does your tool work?

ES-MK: The tool is simple. An alarm goes off if their heart rate elevates significantly. So far, the feedback has been very positive. In addition to communicating pain, it has communicated a subjectivity. We have gotten feedback that the tool has helped remind staff that there is a real person in here, an "I."

In the newest version, a dynamic alarm calculates spikes based on variation for the past 20 minutes, rather than for each day as it did in a pilot study. This way, the threshold adapts to what heart rate the person has throughout the day. It's much more sensitive to things happening in the environment, and it has fewer false positives.

S: Another part of what you're looking at here is these inflammatory cytokines. Why did you choose these markers?

ES-MK: These markers have been **shown to be elevated** in painful conditions, but we're still in an early phase. We don't know for sure that these are good markers for pain specifically, and therefore this is a more experimental part of the project. However, when combining them with heart-rate variability, we think that we will get a good measure of inflammatory changes in the patient. The study aims to look into two subgroups of pain: The cytokine markers and heart-rate variability tell us about chronic pain, and the heart-rate increases tells us about acute pain.

S: How do you see your tool being applied in real-world circumstances?

ES-MK: Our project is a "real-world" study, so we can see the monitoring's real-world applicability directly. Many of our patients already have a lot of equipment: casts to stretch their limbs, to help them stand, medication tubes and feeding tubes. The effects of the treatments and equipment are often unknown, and there is no good way to evaluate the effectiveness of interventions. We hypothesize that this heart-rate tool will improve everyday life for nonverbal patients.

Drug samples:

- Sangamo Therapeutics laid off **27 percent** of its U.S. workforce in the wake of news that two of its big pharma partners, Novartis and Biogen, had ended partnerships to develop gene therapies based on Sangamo's zinc-finger protein modification technology.
- Arbaclofen rescued memory and behavior issues in two out of three different mouse models of 16p11.2 deletion syndrome, according to a **preprint** manuscript posted to bioRxiv this month. Four labs collaborated on the project in an effort to replicate and expand on the results of a 2018 **study**. "This approach is potentially powerful, since behavioral data in mice is notoriously variable and often not reproducible," says **Susanne Schmid**, professor of anatomy and cell biology at Western University in London, Ontario, Canada, who was not involved in the 2018 study or the preprint. A **phase 2 trial** of arbaclofen for children with 16p11.2 deletion is underway. Both the mouse work and the clinical trial involve scientists at the Simons Foundation, *Spectrum*'s parent organization.
- Australian biopharmaceutical company Neurotech International is expanding the uses of its cannabis-based drug **NTI164**, after a **successful phase 1/2 trial** for children with autism. Last month the company announced its plan for a **phase 2 trial** in young people with Rett syndrome. This month it announced it has begun treating participants in a phase 1/2 trial for the **controversial condition** pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS), also known as pediatric acute-onset neuropsychiatric syndrome (PANS).

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

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