A new way of thinking about trials to prevent Huntington's disease

Can we test drugs to delay or prevent the onset of Huntington's disease? New research suggests it's possible

By Dr Jeff Carroll | October 27, 2017 | Edited by Professor Ed Wild

---

A new analysis of clinical data from the TRACK-HD and COHORT studies proposes a way to design of clinical trials designed to delay the onset of HD, rather than treating symptoms after they occur.

What's the history of clinical trials in HD?

Clinical trials are experiments conducted to see whether a new treatment can influence the course, or severity, of HD. The HD community has successfully lots of clinical trials over the last 20 years (nearly a hundred!) – a few of which have identified drugs to improve symptoms (tetrabenazine and deutetrabenazine), but none (yet!) that prevents or slows the onset of HD.

A drug to delay or prevent Huntington's disease would be great. This new research suggests a way of testing such drugs efficiently.

To date, almost all trials of drugs to slow down the disease process have been carried out in people who already have HD symptoms, and only a few small trials have tried to delay or prevent the onset of HD in people who carry the mutation, but don't yet have symptoms.

What’s an endpoint?

To understand why it’s difficult to run prevention trials – and what this new paper teaches us – we need to think about something called an **endpoint**. An endpoint, in a clinical trial, is the outcome we’re trying to study. For many HD studies that are focused on movement symptoms, the endpoint is some score that describes how bad a subjects movement symptoms are. Other endpoints may focus on different things, such as depression in a drug designed to help with mood symptoms, or overall functioning in a drug aimed at slowing progression.

For a trial to be successful, researchers need to define the endpoint of their study ahead of time. Then they run the study, measure their pre-determined endpoint, and determine whether their therapy changed their endpoint at all.

The recent First-HD trial of deutetrabenazine is a good example. The researchers pre-determined that they would measure movement symptoms in groups of HD patients treated with Deutetrabenazine, and defined exactly how much improvement would have to be seen for a successful trial. In the end, the drug did improve symptoms, the trial ‘met its endpoint’, and the FDA licenced the drug for HD.

Now, imagine you want to prevent or delay the onset of HD, rather than treat a symptom. You take your group of people who carry the HD mutation but don’t yet have symptoms. Give them your experimental drug, and then … what? By definition, the volunteers don’t yet have HD symptoms, so there’s no symptoms to observe. How can we tell if the drug is working?

Borrowing from Cancer studies

> **“The researchers were able to show that a reasonably potent drug to prevent HD onset could be tested in fewer than 400 people ”**

This problem isn’t unique to HD - many disease areas have similar difficulties in designing preventative trials. In cancer, for example, the goal of a new treatment might be to delay the coming of some event, like surgery or even death, rather than treating a specific symptoms. Cancer researchers, in particular, have used this kind of clinical trial recently, which goes by the technical name **progression-free survival**.

The math behind progression free survival is a little complicated, but the idea is very simple. The goal of such a study is to establish the average time it takes for some pre-defined event to happen. In HD, that event could be the formal diagnosis of symptoms by a physician. It could also be the time until some other event - like the development of a certain amount of movement symptoms.

Applying this idea to HD, researchers wanting to run a trial to delay HD onset would take two groups of symptom-free volunteers, give one group an experimental drug, give the other group a placebo, and see how long it takes the event to happen in each group.

This kind of design sounds great, in theory, but would it work in reality for HD?

New analysis

Luckily in HD, we have excellent sources of data for researchers to dig into. Two long-term studies of HD mutation carriers - TRACK-HD and COHORT - were designed to track changes in people who carry the HD mutation, including those who do not yet have symptoms. While there were some differences between the studies, the core idea was similar enough between the studies to make useful comparisons.

A team of researchers, led by Jeff Long (University of Iowa) and Sarah Tabrizi (University College London), decided to use these existing datasets to understand whether a **progression-free survival** type of trial would work in HD.

We need to design clinical trials carefully, so they can test drugs effectively in the smallest number of people possible, over the shortest time.

Of course, for this analysis, the researchers don't have a magic drug that will delay the onset of HD. But, they can use the data from TRACK-HD and COHORT in a sort of mock analysis of what would happen if such a drug did exist, and if it had a range of effects - from small to large.

Using their experience from HD trials, the researchers assumed that a trial using these new progression-free survival endpoints would last for 3 years, and that about 1 in 10 of the participants will drop out. Given these assumptions, the researchers were able to show that a reasonably potent drug to prevent HD onset could be tested in fewer than 400 people. That seems really achievable, which is great news.

Take home message

This new analysis teaches us some important things. First - it's important for HD families to get involved in any research they can. The participants in TRACK-HD and COHORT had no idea that this clever new analysis would be used on the data they volunteered to

researchers. The process of research is cumulative, and everything we learn about Huntington's disease from patients enables us to push harder, apply new tools and make new insights.

Second, this research provides excellent evidence that the HD community could successfully complete a **progression-free survival trial**. The community has filled a number of trials as large as 400 people - demonstrating to potential trial sponsors that this something we can achieve.

Meanwhile, the hunt for a drug to test with this sort of trial continues. This year and next are exciting ones for drugs - particularly huntingtin-lowering drugs. Hopefully, before long, a trial to prevent the onset of Huntington's disease will incorporate these new methods for clinical trial design.

Ed Wild, who edited this article, is a principal investigator at UCL Huntington's Disease Centre, where Prof Tabrizi, the senior author of the research discussed, is based. Dr Wild had no involvement in the research and did not discuss the article with Prof Tabrizi or anyone else involved in the work. For more information about our disclosure policy see our FAQ...

GLOSSARY

clinical trial Very carefully planned experiments designed to answer specific questions about how a drug affects human beings

placebo A placebo is a dummy medicine containing no active ingredients. The placebo effect is a psychological effect that causes people to feel better even if they're taking a pill that doesn't work.

cohort a group of participants in a clinical research study
