HDBuzz

Huntington's disease research news. In plain language. Written by scientists. For the global HD community.

Sorry folks, the PRIDE-HD trial did NOT show that Pridopidine slows the progression of Huntington's disease

HDBuzz helps untangle some bold claims about the just-announced results of the PRIDE-HD trial of pridopidine in HD

By Dr Jeff Carroll on September 30, 2016
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A recent press release from Teva Pharmaceuticals has the HD community excited, claiming "Pridopidine Demonstrates Slowing of Progression of Huntington Disease in PRIDE-HD Study". What's pridopidine, and what can we really say about HD progression in patients treated with it?

A brief history of pridopidine in HD

Pridopidine is a drug with a long history in HD. In the course of this history it's had a few different names - including pridopidine, ACR16 and Huntexil. It was developed initially by a small Swedish biotechnology company called Carlsson Research that was subsequently acquired by the Danish biotech, NeuroSearch.

The drug (which we'll call pridopidine in this article) has complex effects on brain chemistry. One thing scientists *thought* they understood was that it seemed likely to help people with HD control their movements. In HD, of course, people have involuntary twitchy movements called **chorea**, but they also have difficulty with voluntary movements, like reaching for a cup or walking down stairs.

PRIDE-HD was originally planned to assess whether pridopidine improved movement function in HD.

To test whether pridopidine could have benefits in HD patients, NeuroSearch conducted two clinical trials. One in North America was called **HART**, and another in Europe called **MermaiHD**. In each trial, several hundred HD patients were treated with pridopidine, or placebo pills. Ultimately, the question for both trials was the same - does pridopidine treatment improve HD patients' movements, compared to people only taking placebo pills?

Unfortunately, both the MermaiHD and HART trials failed to provide conclusive evidence that the drug helped with movement symptoms in HD. In both cases, HD patients who took the drug seemed to do a little bit better than people who didn't, but the difference wasn't large enough to be confident.

Where does Teva come in?

In 2012, pridopidine was acquired by Teva Pharmaceuticals, an Israeli pharmaceutical giant. The job of global head of research at Teva had just been taken by long-time HD researcher Dr Michael Hayden of the University of British Columbia.

Teva quickly started planning another trial. The goal of this third trial was to conclusively demonstrate whether or not pridopidine helps HD patients with their movements.

The trial was called **PRIDE-HD**. It was originally planned to run for 6 months, and included higher doses of pridopidine than used in HART and MermaiHD, in hopes that higher doses of drug may provide greater benefit than lower ones.

What are the results?

As we've discussed previously on HDBuzz, each clinical trial needs to have what researchers and regulators call a **primary endpoint**. It's a bit like calling a complex shot in a pool game – you need to specify **ahead of time** what effects you think your drug is going to have, before you take your shot. This requirement to clearly state your intentions ahead of time ensures we're not distracted by cool, but potentially just-by-chance, things that happen in the course of a trial.

For the PRIDE-HD study, Teva specified that they would investigate whether treatment with pridopidine improved something called the **total motor score**. On September 18th 2016, at the European Huntington Disease Network meeting in The Netherlands, Dr Hayden presented a first-pass analysis of the results of this study.

Unfortunately, pridopidine failed to meet its primary endpoint in PRIDE-HD. Overall, patients treated with pridopidine did not have better total motor scores than patients treated with placebo. This is the same outcome as the two previous studies of pridopidine in HD.

If that's the bottom line, how come Teva's announcement and press release said "Pridopidine Demonstrates Slowing of Progression of Huntington Disease in PRIDE-HD Study" in its first line?

Symptomatic vs. disease-modifying treatment

Let's back up a second, because this trial was run in a slightly unusual way.

As the PRIDE-HD study began, Teva continued their work investigating pridopidine in the lab. That's good science - while we test drugs in people, we should continue to investigate them in the lab to understand them as best we can. The details are a bit complicated, but based on this new

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work in the lab, researchers at Teva now think that pridopidine might work in the brain in a way that no one had predicted.

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The implication of Teva's new work in animals is that pridopidine could potentially protect against the actual harm done by the HD mutation, rather than just treating symptoms after they develop.

Why is this an important distinction?

Think about the common cold. It's caused by infection with a virus. To help, we could either treat all the symptoms of a cold (headache, fever, sneezing, coughing), or we could try to prevent the virus from ever infecting someone in the first place so that none of those symptoms ever develop.

This distinction exists in HD as well. We already have treatments that are designed to reduce the impact of **symptoms** on a patient's quality of life. These include things like antidepressants for depression and anxiety, and tetrabenazine for chorea. We don't think those treatments slow down the course of HD, but they make a very important impact on how patients feel and function in daily life.

Other treatments – which we **don't** have for either HD or the common cold – would aim to treat the disease process itself, not just symptoms. For a cold, that might mean a drug that prevents a virus from ever infecting our cells. In HD, a treatment like that would stop brain cells from malfunctioning and dying. A treatment like that could ultimately prevent the disease from developing in the first place.

To distinguish these kind of approaches from symptomatic ones, we call them **disease-modifying treatments**. Essentially, they will slow the progression of Huntington's disease.

Proving disease modification is hard!

These progression-slowing treatments are clearly a major goal of HD researchers, but they are fiendishly hard to develop. To understand why, we have to remember that symptoms of HD develop over decades, and it's very difficult to figure out whether an improvement in symptoms is because of a direct effect on the symptoms themselves, or because the disease process has been slowed down.

Clever scientists and regulators have actually come up with a few ways to address this problems. Without getting lost in the details, we'll just say that there are ways to set up a clinical trial to precisely test whether a drug can slow disease progression, rather than just improving symptoms. For people interested in researching this in more detail, these types of studies are called **delayed start** or **washout** trial designs.

For symptom-treating drugs, it's much easier. We just need to give patients a drug, and then measure whether that drug makes the particular symptom get better. Doctors are pretty good at measuring things like movement, and even more difficult things like depression and thinking problems in HD.

So, is pridopidine modifying HD progression?

With that scintillating discussion into clinical trial design complete, we can now try to unpack Teva's suggestion that pridopidine treatment led to a "slowing of progression of Huntington disease".

Running a clinical trial is a bit like a game of pool. That fancy shot is much more impressive if you declared what was supposed to happen in advance.

The first thing to note is that the PRIDE-HD study was **not** structured in a way that could ever let researchers actually measure slowing of disease progression - it did not have a **delayed start** or **washout** design. So, there's no way that the data we have so far **could** tell us if pridopidine slows progression - just whether it made some symptoms better.

As we discussed above, the original design of the PRIDE-HD study was strictly focused on showing that pridopidine provided movement benefits to HD patients. However, Teva – perhaps motivated by its new lab results suggesting the drug might actually protect the brain – decided to change the structure of the PRIDE-HD study while it was running.

Teva successfully asked regulators to change the design of the PRIDE-HD study, in two important ways. First, they decided to extend the duration of treatment from 6 to 12 months. If we're looking for slowing of disease progression, having a longer observation time might help us to tell if we're really changing the course of disease.

Secondly, Teva added another endpoint to their study. The primary endpoint remained the same – the study was designed to establish whether pridopidine improved movement symptoms of HD, which it didn't do. But Teva decided they would also, after 12 months of treatment, examine something called the **Total Functional Capacity** of patients treated with pridopidine.

Total Functional Capacity sounds complicated, but it's actually very simple. To measure Total Functional Capacity, a doctor simply asks an HD patient how well they're managing with some normal activities – things like employment, chores around the house, finances and so on. A higher Total Functional Capacity score means that a patient is doing a better job maintaining their normal activities, which tend to become more and more impaired as HD progresses.

So, does pridopidine improve functional capacity?

At the lowest dose, HD patients treated with pridopidine seemed to be functioning better overall at 12 months than patients treated with placebo. Their Total Functional Capacity scores were 'significantly' different. At the three higher doses of pridopidine, this effect was not observed.

In a press release, Spyros Papapetropoulos, Teva's VP Clinical Development, Neurodegenerative Diseases, was quoted as saying: "Slowing down the progression of this disease **has proven to be impossible until now**. These findings give us a reason to believe

we may be finally making progress in slowing deterioration of disease" (emphasis ours). This statement suggests that while it has so far been impossible to slow the progression of HD, the PRIDE-HD study has done so.

Researchers at Teva have decided that they believe that an improvement in total functional capacity means that HD was progressing more slowly in patients treated with pridopidine. Dr Hayden, for example, told HDBuzz, "we believe … functional decline is synonymous with progression". We disagree, and we **don't** think the difference is just semantics.

We think there are multiple ways that patients taking a drug could come to **function** better, without the drug **changing the course of the disease**.

For example, a drug that improved apathy or anxiety in HD patients could help them function better in daily life. Improving apathy or anxiety in HD would be wonderful things for HD patients - but treating them wouldn't necessarily change the course of the disease. Eventually, the process of brain-cell death would overtake the symptom benefits of the drug.

A controversial announcement

For this reason, we disagree with Teva's interpretation of the PRIDE-HD data, or at least the data we've seen so far.

What's more, we don't think HD patients and family members can reasonably be expected to hear "slowing down the progression" and understand that what's meant is "stabilising a functional score in a way that could be explained by a drug that just improves symptoms".

We're not alone. Many HD researchers we've spoken to were unsettled to hear the results presented being described as slowing of progression.

> "The results of PRIDE-HD are interesting and we look forward to hearing more when the full results are released. We also completely agree with Teva that another trial is a good idea."

Dr Karen Andersen, Director of the HDSA Center of Excellence in Georgetown, Washington DC, said, "The PRIDE-HD results on Total Functional Capacity are interesting, but I think it's risky to talk about 'slowing progression', as this could easily be misinterpreted as slowing the underlying process of brain degeneration. That's the big news for which HD families have been waiting – but PRIDE-HD was not designed to answer this question."

Dr Martha Nance, Medical Director of the Huntington's Disease Center in Minnesota for 25 years, said, "The bottom line is that PRIDE-HD didn't meet its endpoint of improving movements. The other results presented need to be read with caution, especially the claim about slowing progression. We don't want to raise false hopes, but need instead to be as certain as we can about our findings and interpretations as we move forward."

Dr Neil Aronin, a senior HD researcher at University of Massachusetts added, "Teva's announcement and data don't really give us the information we need to say whether the drug

had any effect. There seems to be a lot of variability in the data which makes drawing conclusions difficult. That highlights how hard it is to study HD. Reproducible, robust, objective measures are hard to come by in a disease of this kind. I believe that is a real message of the study. I think Teva will need to include some objective measures of brain change in future trials if they want to show that pridopidine slows progression."

"Science is hard," notes **Marcus Munafò**, a methodological expert at the University of Bristol, "and unfortunately it's common for trials to fail to show a benefit on their pre-specified endpoints. For understandable reasons, this is often followed by careful combing through the results for any possible new leads. Sometimes, these after-the-event announcements lead to other trials – but sadly there's a long history of those trials failing, too, which is why we should be careful not to read too much into those new leads until they've been properly tested."

Take-home message

To show definitively that pridopidine slows the progression of HD, Teva needs to run a trial with the appropriate design to provide that kind of evidence. Interestingly, this doesn't seem to be on the cards. In an email to HDBuzz, Dr Papapetropoulos stated: "we currently do not intend to pursue a disease modification path … nor [do] we claim that Pridopidine showed an effect in modifying the course of the disease in PRIDE-HD". That's a very helpful clarification, and we appreciate Teva's taking the time to issue it.

It leaves us a little unclear what Teva is saying about their drug, though. If pridopidine really slows down the progression of HD, at the level of protecting neurons from damage, a specially-designed trial would be needed to prove it. We know how to do that kind of trial - the delayed start or washout design we mentioned earlier. On the other hand, if pridopidine 'only' helps patients function better, **that's still great**, and another trial to prove it is a good idea.

Let's be clear

We agree with Dr Aronin that the road to effective treatments for HD is a long and bumpy one. We need all the help we can get, and we're really glad Teva is bringing its motivation, resources and thinking power to the fight. The results of PRIDE-HD are interesting, for both movements and function, and we look forward to hearing more when the full results are released. We also completely agree with Teva that another trial is a good idea to look at the possible effect on HD patients' functioning. We just wish the language used to describe the results, and Teva's plans, had been a bit clearer from the outset.

Everyone involved in the PRIDE-HD study hoped that it would show clear benefits for movement problems in HD. It didn't, but as one door closes another often opens. Data gathered from the brave volunteers in this study point us in new directions for future trials with a better chance of figuring out whether it helps them function better.

Jeff Carroll used to study and work in the laboratory of Michael Hayden, who is now Head of R&D at Teva Pharmaceuticals. Ed Wild is an investigator in the Legato-HD study, a trial of a

different drug currently being run by Teva. Neither has any financial conflict relating to this article. *For more information about our disclosure policy see our FAQ...*

Glossary

Total Functional Capacity A standardized rating scale for function in HD, used to assess capacity to work, handle finances, perform domestic chores and self-care tasks

neurodegenerative A disease caused by progressive malfunctioning and death of brain cells (neurons)

primary endpoint The main question asked in a clinical trial

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

neuron Brain cells that store and transmit information

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.

chorea Involuntary, irregular 'fidgety' movements that are common in HD