Huntexil for symptoms of Huntington's disease: where are we now?

Two clinical trials in Europe and the USA have suggested a new drug, Huntexil, might improve movements in HD. The nex

x A new article has been published with updated information on this subject: FDA: further trial needed for Huntexil approval in HD

By Dr Ed Wild November 16, 2010 Edited by Dr Jeff Carroll

2010 was a big year for the small Danish pharmacology company NeuroSearch and its experimental drug, Huntexil, which aims to improve the movements and coordination of people with HD symptoms. What have NeuroSearch’s two clinical trials - MermaiHD in Europe and HART in the USA - told us about the possible benefits of Huntexil - and what is likely to happen next?

What is Huntexil?

Huntexil - also known as ACR16 and pridopidine - is described as a dopamine stabilizing drug. Dopamine is a signaling chemical that acts in the brain regions that are important for movement and coordination. In Parkinson's disease, there is an obvious problem of a lack of dopamine, and in Parkinson's, replacing the dopamine provides symptomatic relief, at least for a time. The problem in HD is more complicated: in some brain areas there seems to be a lack of dopamine signaling, while elsewhere there may be too much.

Problems with balance and coordination are currently very difficult to treat in HD

This imbalance is mirrored by two common patterns of movement problem that often exist at the same time in HD patients. The first is involuntary, extra movements called chorea. The second is a loss of voluntary movements, causing stiffness, poor coordination, balance problems and falls.

Treatments that decrease dopamine signaling are already available for the symptoms of unwanted extra movements - drugs like tetrabenazine, risperidone and olanzapine. But these can worsen stiffness, balance and voluntary movements. Since many patients find the extra movements much less troublesome than the loss of voluntary movements, existing treatments aren't ideal for many patients. However, there are no treatments currently available that are effective in improving voluntary movements.

This is where Huntexil comes in. As a dopamine stabiliser, it is said to increase dopamine signaling in brain areas where there isn't enough dopamine, and decrease it in areas with too much dopamine, so that overall the effect is to return the brain's dopamine levels towards normal.

The MermaiHD Study

The MermaiHD study was a joint project of NeuroSearch and the European HD Network. 437 HD patients were enrolled in eight EU countries, with each patient studied for six months. Two different doses of Huntexil were tested, along with a placebo pill (a pill containing no drug). The study was 'double-blind', meaning that neither the patients nor their doctors knew which treatment was being used.

Effects of Huntexil were assessed using a modified movement score (called mMS) focused on voluntary movements. In the group taking the higher dose of Huntexil, there was a small drop in the score, suggesting some improvement after six months.

Statisticians use a technique called **significance testing** to try to determine whether a result like this might have happened by chance or shows a genuine effect of the drug. Significance testing measures how 'surprising' a result is: the more surprising, the more likely it is that we are dealing with a genuine improvement.

Better treatments for HD symptoms could make a big difference to some patients

Unfortunately the improvement in voluntary movements was not 'surprising' enough to be declared **statistically significant**, according to the criteria set in advance by the trial planners and regulatory agencies - so the study narrowly missed demonstrating an overall benefit on voluntary movements.

However, an improvement in **overall** motor function was seen in patients taking Huntexil, which **was** statistically significant, and a later statistical analysis that compensated for differences in CAG repeat length on **voluntary** motor function did reach the level of 'surprise' needed to declare the result statistically significant.

Overall, though it would have been nice to see a larger effect of the drug and a 'significant' result on the main measure of success, the results of the MermaiHD trial were seen as encouraging because no drug has been shown to improve voluntary movements in HD before.

The HART Study

HART was a followup study that NeuroSearch conducted alongside the Huntington Study Group. With 227 volunteers over 3 months, it was smaller and shorter than MermaiHD, because it was designed not to prove whether Huntexil is effective, but to test several different doses to see which dose was likely to be best.

By testing several different doses, the study is also able to look for a 'dose-response relationship' - that is, whether higher doses produce a bigger improvement.

Like MermaiHD, patients treated in the HART study ended up with movement scores that were better on average. Again, the study didn't show a significant improvement in **voluntary** functioning that had been hoped for - but that is not surprising since it was smaller and shorter. A dose-response relationship was found, which suggests that

the drug is acting in the way we would expect.

Neurosearch is a pharmaceutical company based in Denmark

NeuroSearch have recently pooled together all the data from the two trials and in this 'meta-analysis' there **was** a significant improvement in voluntary motor function after six months.

What happens now?

Huntexil has now been tested in two different groups of patients and seems to be safe, with few side effects reported. That is a very good start for any drug. The best result would have been for the main measure in the MermaiHD trial to be positive, which it narrowly missed. But the improvements seen in both trials in total motor function, and the encouraging results for voluntary function from the later analyses, suggest that Huntexil might turn out to be beneficial for HD symptoms.

Scientists are always cautious about new treatments, because experience with them in real life can sometimes throw up problems that clinical trials don't reveal. One thing to bear in mind is that the improvements seen in these trials are measured are an average for the whole group tested. In 'real life', Huntexil might turn out to be very effective in some patients and less effective in others.

It's also worth noting that at the moment Huntexil is only seen as a possible treatment for symptoms of HD, rather than being able to slow down the damage to brain cells that causes the disease. If Huntexil does have such an effect, it will take a long time - possibly several years - to show it.

In an interview with HDBuzz, the Head of Clinical Science at NeuroSearch, Joakim Tedroff, said he remains cautiously optimistic about getting Huntexil licensed and available to HD patients. "I think it probably will be licensed", he said. The licensing process is always slow, taking several months or years, even for a drug that has proven itself beyond doubt. NeuroSearch now has to convince the drug licensing agencies that the combined evidence from its trials is compelling enough to issue a license for Huntexil.

Whatever happens, HDBuzz will keep you posted with the latest news.

The authors have no conflicts of interest to declare. For more information about our disclosure policy see our FAQ...

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Huntington Study Group Euro-HD Network NeuroSearch press release on the MermaiHD trial (March 2010) NeuroSearch press release on the HART trial (October 2010) Latest NeuroSearch press release with future plans (December 2010)

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- Glossary
- **statistically significant** Unlikely to have arisen by chance, according to a statistical test
- **significance testing** A method used by statisticians to try to decide whether the result of a study or trial is genuine or likely to have happened by chance
- **Parkinson's Disease** A neurodegenerative disease that, like HD, involves motor coordination problems
- **meta-analysis** Combining the results of several different studies and analyzing them together, to increase their ability to answer a particular question.
- **CAG repeat** The stretch of DNA at the beginning of the HD gene, which contains the sequence CAG repeated many times, and is abnormally long in people who will develop HD
- **dopamine** A signaling chemical (neurotransmitter) involved in movement control, mood and motivation
- **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
- Read more definitions in the glossary

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