

TETRA-HD Press Release

Drug Aimed at Huntington's Eases Chorea, the Disease's Hallmark Feature

February 13, 2006...A drug widely available in Europe and Canada – but not the United States – eases one of the most disabling symptoms of Huntington's disease, involuntary writhing movements known as chorea, according to a study in the Feb. 14 issue of the journal *Neurology*.

The medication, tetrabenazine, is currently being reviewed by the U.S. Food and Drug Administration. If approved, the medication would be the first authorized by the agency expressly for the treatment of Huntington's disease, which affects about 30,000 people in the United States.

In a randomized, controlled study conducted in 84 patients at 16 sites around the nation, doctors found that the medication cut down involuntary movement on average by about 25 percent, with many patients experiencing a greater improvement. Overall, patients who received the medication were six times as likely to be considered by their doctors to have improved considerably, compared to participants who received a placebo.

"Neuroleptic drugs like haloperidol (Haldol) are currently in widespread use in the United States to suppress chorea, but the effect of these drugs on chorea has never been studied in a systematic way, and they have a number of troublesome side effects, such as blunting of personality, loss of voluntary movement, and hindering balance. Our study showed that tetrabenazine, when appropriately dosed, can decrease chorea without those side effects," said Frederick J. Marshall, M.D., a neurologist at the University of Rochester Medical Center who led the study conducted by the Huntington Study Group. The study was funded by Prestwick Pharmaceuticals of Washington, D.C., the company that owns the rights to develop and sell the medication in the United States.

Tetrabenazine was originally developed in the 1950s to treat psychosis, but was quickly pushed aside by more effective medications. But doctors in the United Kingdom found it to be effective to treat the excessive involuntary movements of Huntington's, and it is approved for use in several nations. In the United States, tetrabenazine is designated as an "orphan drug" by the FDA since it's targeted to a disease directly affecting fewer than 200,000 people in the nation.

The symptom that tetrabenazine treats – involuntary, writhing movements of the limbs, face, and sometimes the entire body – is the hallmark symptom of Huntington's disease, an inherited neurodegenerative disorder that worsens as brain cells known as medium spiny neurons are killed off by a mutant protein. The disease brings with it an array of other difficulties as well, including cognitive problems, changes in personality, and psychiatric problems like depression. As many as one-quarter of patients with the disease attempt suicide, and many suffer from progressive cognitive decline. Unlike Alzheimer's disease, where patients usually lose their memory and insight into their

disease at some point, most Huntington's patients understand exactly what is happening to them throughout most of their illness.

The disease usually strikes people in their 30s and 40s, though some patients are affected as early as childhood, while others aren't affected until their older years. Virtually everyone with the disease had a parent with the disease, and children of a person with Huntington's have a 50-percent chance of inheriting the disease. Thirteen years ago the gene that causes the disease was identified by scientists, and now a simple blood test can tell people whether they will develop the disease or not. But since there is no way known to prevent the disease or slow its progression, and for other reasons as well, many patients decline the test, instead waiting to see if they develop symptoms like the ones they witnessed in a parent. Patients usually live for 15 to 20 years after the onset of symptoms.

Viewed simply, in some ways Huntington's disease is the opposite of Parkinson's disease, where damage to the neurons that produce dopamine hinders a person's ability to move and cause other symptoms. In Huntington's, too many dopamine signals result in random, uncontrollable movements. Tetrabenazine inhibits a molecule known as vesicular monoamine transporter 2 (VMAT2), an action that ultimately blocks the release of dopamine.

"This is not a wonder drug for Huntington's. It doesn't address the psychiatric or cognitive problems, for instance. But there are some patients for whom chorea is clearly a devastating feature of the illness," said Marshall, an associate professor of Neurology who is chief of the University's Geriatric Neurology Unit. "Easing chorea could help patients with tasks they normally struggle with, such as eating, driving, grooming, and walking.

"As a physician, I have no doubt that this medication can be very helpful to some patients. If the drug is approved, physicians will need to work closely with patients and their caregivers to adjust the dosage safely. About a quarter of patients reported sedation, fewer than 10 percent of patients had motor restlessness, and fewer than 5 percent had motor slowing or depressed mood. Side effects generally resolved with downward adjustment of the dosage. Of concern, one patient committed suicide during the study. Because of the high rate of suicide attempts in patients with Huntington's disease, all patients deserve close follow-up."

The study was carried out by the Huntington Study Group, a non-profit, cooperative group of Huntington's disease experts from medical centers throughout North America, Europe and Australia who are dedicated to improving treatment for persons affected by the disease. HSG is supported by the Huntington's Disease Society of America, the Hereditary Disease Foundation, the Huntington Society of Canada, and the High Q Foundation. More information is available at www.Huntington-Study-Group.org.

HSG is based at the University of Rochester Medical Center, which is home to one of the world's top groups of doctors specializing in Huntington's disease. The study was run through the Department of Neurology's Clinical Trials Coordination Center, where physicians design and conduct large multi-site studies of potential new treatments for

diseases like Parkinson's disease, Huntington's disease, and neurological disorders related to HIV.

Marshall is part of a team of doctors, scientists and nurses that treats people from more than 200 families from throughout the Northeast with the disease. He also specializes in the treatment of patients with Parkinson's and Alzheimer's diseases.

"There's something compelling about this disease," said Marshall. "I feel very close to my patients with Huntington's disease. I'm inspired by them. To a person, they are courageous and compassionate. Even in the face of something as difficult as Huntington's disease, my patients preserve a sense of dignity and grace.

"These are people who live every day with the burden of knowing that there is not yet a cure, and that their closest loved ones are themselves at 50/50 risk of getting the disease. Many of them grew up caring for a parent or a sibling with the illness, so they are fully aware of the symptoms and signs of the disease as it progresses. Yet, even in the face of this, they maintain optimism and a sense of humor. It is an honor to be part of the extended community of patients, families, and researchers trying to find a better way forward."

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