

Tetrabenazine as Antichorea Therapy in Huntington Disease: A Randomized Clinical Trial

By Lisa J. Bain – October 2007

Tetrabenazine has been widely used in Europe and Canada to treat [chorea](#) in people with Huntington's disease (HD). However, it had never gone through the rigorous testing required by the Food and Drug Administration (FDA) to be approved for use in the United States. Clinical experience suggests that tetrabenazine is associated with fewer troublesome side effects than other drugs, called [neuroleptics](#), that are used to treat chorea. This may be because tetrabenazine acts by a different mechanism than those drugs.

Neurologist Frederick J. Marshall of the University of Rochester School of Medicine and Dentistry was the principal investigator of a clinical trial designed to test the effectiveness and safety of tetrabenazine. The results of that study were published in the journal *Neurology* (February 2006, *Neurology* 66: 366-72) and the FDA is currently reviewing the data to determine whether the drug will be approved for use in HD patients in the United States.

Who took part in this study?

This study was conducted under the auspices of the Huntington Study Group (HSG), a cooperative group of HD clinicians from around the world. For this particular study, 16 HSG sites in the United States enrolled 84 people with HD who exhibited chorea as one of their symptoms. In addition to having chorea, all the participants had a family history of HD and had undergone genetic testing that confirmed the presence of the HD gene.

What did the participants do?

Volunteers for this study agreed to take part in a double-blind, randomized, placebo-controlled trial. This meant that participants might get a [placebo](#) instead of tetrabenazine, but that neither they, nor the clinicians who were providing the drug, would not know which they were getting until the trial was over. Twice as many participants received tetrabenazine as placebo. As part of the trial, participants also agreed to undergo examinations just before the trial began (baseline) as well as at regular intervals for the 12 weeks that the treatment was given. A week after the treatment was stopped, subjects returned for a final exam. These examinations included a physical exam to evaluate vital signs (blood pressure, etc.) and whether they had difficulty with certain kinds of movements, such as finger tapping, walking, and swallowing. In addition, participants completed questionnaires to evaluate sleepiness, depression, and difficulty with daily activities, such as bathing and dressing themselves. Subjects were also videotaped at the end of the treatment phase, and again after the drug was withdrawn, to see whether their chorea returned.

What did the researchers do?

The study was designed primarily to determine the optimal dose of tetrabenazine and to determine if it was effective and safe for this group of subjects. As the dose was increased gradually over the first 7 weeks, the investigators monitored subjects carefully for side effects and cut back on the dose if necessary. An independent group of physicians and statisticians who were not part of the study group and had access to the “unblinded” results (meaning that they knew which participants received placebo and which received tetrabenazine) also monitored the safety aspects of the trial to make sure that any drug-related side effects were recognized immediately. This data safety monitoring committee would have had the authority to halt the trial if any significant adverse effects were noted.

What did they learn?

Interestingly, chorea improved in both the placebo group and the group receiving tetrabenazine, however the improvement was slight in the placebo group and was much greater in those receiving tetrabenazine. On average, patients receiving tetrabenazine had almost a 25% reduction in chorea compared to baseline. Participants receiving tetrabenazine also scored significantly higher on an assessment called the “Clinical Global Impression” scale, which takes into account a person’s overall treatment response rather than simply the change in chorea. Forty-five percent of participants receiving tetrabenazine had more than minimal global improvement compared to about 7% of those receiving placebo.

Tetrabenazine resulted in a somewhat higher incidence of adverse effects, although Dr. Marshall said the drug was “generally well tolerated.” Participants receiving tetrabenazine reported more sleepiness or insomnia, and one participant committed suicide. While he does not believe the suicide was related to tetrabenazine, Dr. Marshall said that the risk of suicide in HD remains a concern. The rate of suicide in HD patients is higher than in the overall population, so clinicians must always take special care to monitor and treat patients for depression regardless of the treatments they are receiving. Measures of depression during this study suggest that mood improved more in the placebo-treated subjects, but that tetrabenazine treatment also was associated with an improvement in mood compared to subjects’ baseline scores.

As expected, when the drug treatment stopped at the end of the trial, chorea returned rapidly. Since the treatment was given for only 12 weeks, the study did not provide information about effectiveness or safety of the drug if given for a long period of time.

Why is this study important?

This study provided the data required by the FDA to consider approval of tetrabenazine for the treatment of chorea in people with HD. Patients who are already taking tetrabenazine through a research study or some other mechanism are able to obtain the medication from the European manufacturer, said Dr. Marshall, “But it’s very challenging right now to get access for new patients because it’s under FDA review.”

Prestwick Pharmaceuticals, the U.S. manufacturer of tetrabenazine, received an “approvable letter” from the FDA in March, 2006, which required them to provide

additional information before a review committee would approve the drug; however, at this point the review committee has still not convened and patients and clinicians are still waiting for a decision about whether tetrabenazine will be approved.

Were there any surprises in this study?

Dr. Marshall said that the results of this study were not at all surprising. “We were delighted by the results because they confirm that tetrabenazine was quite effective for the treatment of chorea.”

What’s next?

The HSG has extended this trial to learn more about the long-term effectiveness of tetrabenazine. Neurologist Samuel Frank of Boston University Medical Center presented data at the 2007 American Academy of Neurology Meeting, which showed that with continued treatment, tetrabenazine maintains its anti-choreic effect for up to 80 weeks. Dr. Frank said that in this study, as with the original study, tetrabenazine was well tolerated and only six subjects stopped treatment due to side effects. Sleepiness, depression, anxiety, and insomnia were again the most frequently reported side effects, although problems with sleepiness and insomnia tended to get better over time.

Chorea – The involuntary writhing movements that are a common and disabling symptoms of HD.

Neuroleptics – A class of drugs given to treat psychosis. They have a calming, tranquilizing effect, and may also suppress chorea in people with HD. They are sometimes associated with severe side effects.

Placebo – a pill or substance made to look like a drug but that actually has no active ingredient. Sometimes the placebo is merely a sugar pill. In a placebo controlled trial, the placebo is delivered in a form that looks exactly like the study drug so that the participants will not know whether they are receiving the real thing or not.