EDITORIAL

Deutetrabenazine for Treatment of Chorea in Huntington Disease

Michael D. Geschwind, MD, PhD; Nick Paras, PhD

In this issue of *JAMA*, the Huntington Study Group (HSG), First-HD study investigators, reports findings from a randomized trial examining use of a deuterated form of tetrabenazine, called deutetrabenazine, for treatment of chorea in patients with Huntington disease.[1] Tetrabenazine, a vesicular monoamine transporter type 2 inhibitor that depletes monoamines including dopamine, is used worldwide for the treatment of chorea and dystonia. Tetrabenazine was approved by the US Food and Drug Administration (FDA) for the treatment of chorea in Huntington disease, based on a prior HSG study.[2]

Related article page 40

Tetrabenazine is usually effective for management of chorea in Huntington disease, although treatment is sometimes limited by peak-concentration adverse effects, such as somnolence, depression, and anxiety. By exchanging certain hydrogen atoms in tetrabenazine with the heavier hydrogen isotope deuterium, degradation of the drug and its active metabolites is impeded, leading to an increase in their circulating half-lives and thereby preserving the duration of therapeutic benefit while decreasing the required dose and the associated peak concentration.[3] Theoretically, deutetrabenazine should work by the same mechanism as tetrabenazine, but with a different pharmacokinetic profile.[3,4]

In this randomized, double-blind, placebo-controlled trial,[1] 90 ambulatory patients with Huntington disease were enrolled from 34 HSG sites in the United States and Canada and randomized 1:1 to receive deuterated tetrabenazine (n = 45) or placebo (n = 45). Eligible patients were required to have been diagnosed with Huntington disease based on genetic testing for CAG (cytosine-adenine-guanine [amino acid sequence]) repeats (>36 CAG repeats) and have a total functional capacity score of 5 or higher on a scale of 13 and 8 or higher on the total maximal chorea score of the Unified Huntington Disease Rating Scale (UHDRS) motor examination. The total functional capacity score assesses functional capacity in 5 areas: occupation, finances, domestic chores, activities of daily living, and care level, with each category scored from 0 to 2 or 0 to 3 for a maximum of 13 points, with higher scores indicating better function. A score less than 5 indicates moderate to severe impairment of function, requiring a full-time caregiver. The total maximal chorea score rates chorea in 7 body regions each on a 0 to 4 ordinal scale, for a maximum score of 28, with higher scores indicating worse chorea. A score of 8, for example, might indicate slight and intermittent to mild chorea diffusely or more severe focal chorea.[5]

Patients increased the study drug gradually over 8 weeks starting at 6 mg/d (divided twice daily) for the first week and then increased weekly by 6 mg/d until either the chorea was adequately controlled, a clinically significant serious adverse event occurred, or the maximal dose of 48 mg/d was achieved. The final dose was maintained for an additional 4 weeks for a total of 12 weeks, followed by a 1-week washout and reevaluation for safety and chorea.

For the primary outcome, the total maximal chorea score (higher scores represent worse chorea), measured from baseline to maintenance therapy (average of weeks 9 and 12 visits) was reduced by 4.4 points—from a mean (SD) of 12.1 (2.7) to 7.7 (3.9) in deutetrabenazine group—compared with 1.9 points—from a mean (SD) of 13.2 (3.5) to 11.3 (4.1) in the placebo group. The absolute difference of a 2.5-unit (95% CI, 1.3-3.7) improvement in the treated group was statistically significant ($P < .001$). The deutetrabenazine group also showed significant improvement in 3 of 4 prespecified secondary end points. There was a greater proportion of patients who were "much" or "very much" improved on the Patient Global Impression of Change (PGIC) (51% vs 20%, $P = .002$) and on the Clinical Global Impression of Change (CGIC) (42% vs 13%, $P = .002$) in the deutetrabenazine group than in the placebo group. For the 36-Item Short-Form (SF-36) physical functioning subscale scores, the deutetrabenazine group had improvement with a treatment effect of −4.3 (95% CI, −8.3 to −0.4; $P = .03$). The improvement on the Berg Balance Test was not significantly different between the groups. There was also slight but significant improvement in dystonia.

There were no significant differences in safety measures, except the deutetrabenazine group had some improvement in swallowing and mild weight gain. Adverse events occurred with similar frequency between groups, were generally mild to moderate, and led to dose reductions for 3 patients (6.7%) per group. Both groups had a single serious adverse event, leading to drug suspension. The numbers of patients reporting depression or agitated depression were not different nor were depression or anxiety scales between study groups, although somnolence and diarrhea occurred more frequently among patients in the deutetrabenazine group.

As the authors note, the minimal clinically important difference for the primary outcome of the change in total maximal chorea score has not been determined, so the clinical relevance of the findings is not definitive. Patient-reported outcomes, however, were supported by those assessed by the clinician, suggesting that the improvement observed might be clinically meaningful. Thus, deutetrabenazine appears to

be helpful in treating chorea of Huntington disease over 12 weeks and shows some improvement in chorea with no significant adverse effects compared with placebo.

This well-done, clearly presented study by the HSG[1] shows that compared with placebo, twice-daily deutetrabenazine results in modest reductions in chorea at 12 weeks. From this current study, however, it is not possible to determine how this drug compares with tetrabenazine. Comparison of the data from the current deutetrabenazine trial[1] with the prior tetrabenazine trial[2] is limited by several important factors, including that patients in the deutetrabenazine trial overall had worse motor symptoms as measured by the total maximal score (approximately 2 points worse at baseline, approximately 12 in the deutetrabenazine trial compared with approximately 10 in the tetrabenazine group).[2] With this important caveat, however, the results of the studies appear similar in terms of efficacy. In the tetrabenazine study, there was a 3.5-unit improvement (23.5% reduction) in the total maximal chorea score compared with 2.5-unit improvement (21% reduction) in the current deutetrabenazine trial. Similarly, patients in the tetrabenazine trial who received the active drug (compared with placebo) had more subjective global improvement based on clinician's assessments, but unlike the patients receiving active deutetrabenazine, they had more adverse effects, including more withdrawals, increased somnolence and depression, and slightly worse performance on some cognitive scales.

In addition to a more favorable adverse effect profile, the twice daily dosing of deutetrabenazine is preferred to the 3 times daily dosing generally required for tetrabenazine.[2] This is particularly true for patients with Huntington disease who might have difficulty with medication adherence due to cognitive impairment, swallowing problems, and behavioral issues.[6] From a clinician's standpoint, an ideal trial might have had 3 groups comparing deutrabenazine, tetrabenazine, and placebo to show that the drug is more effective than placebo but also a head-to-head comparison of deutetrabenazine against tetrabenazine (noninferiority), as was recommended by one of the developers of this compound.[4] Noninferiority trials, however, require much larger sample sizes, are more costly, and have a higher likelihood of an inconclusive result.[7-9] These factors in addition to the FDA's typical requirement that a drug to show improved efficacy over placebo likely influenced the choice to test deutetrabenazine in a superiority trial against placebo.[9,10] Furthermore, the FDA approved tetrabenazine for treatment of chorea in Huntington disease essentially based on a single placebo-controlled trial with 90 patients[2] with efficacy data similar to this study. Assuming deutetrabenazine is not priced to be significantly more expensive than tetrabenazine, the favorable profile of deutetrabenazine would offer an additional option for patients and clinicians, so physicians may consider prescribing deutetrabenazine over tetrabenazine, if and when the drug is approved.

The current study by the HSG should be interpreted in light of several caveats and limitations. Although the minimal clinically important difference for the total maximal chorea score is not established, some data suggest that the effect sizes reported in this study and in the prior tetrabenazine trial are clinically meaningful. In both studies, subjective improvement was noted by patients or clinicians, and in clinical practice, tetrabenazine clearly reduces chorea. In addition, because the duration of the trial was relatively short, consisting of only 12 weeks of therapy, the sustainability of benefit over a longer time course is not known. These and other issues regarding a comparison of deutetrabenazine and tetrabenazine should be addressed by the ongoing ARC-HD (Alternatives for Reducing Chorea in Huntington Disease; NCT01897896) study,[11] which will examine the safety and tolerability of patients with Huntington disease taking tetrabenazine and switching to deutetrabenazine and will also include patients from this current deutetrabenazine study who chose to switch to open-label deutetrabenazine.

Some other remaining issues include why deutetrabenazine had a slight benefit in dystonia on the total maximal chorea score but was associated with increased diarrhea, both of which were not observed in the tetrabenazine trial.[2] Some of these issues will likely be addressed in the ARC-HD study.[11] The FDA recently requested examination of blood levels of certain metabolites,[12] presumably to confirm what had been previously shown in a smaller study that the active deuterated metabolites are maintaining a sufficient plasma concentration and for an extended time.[3]

The clinical trial reported by the HSG in this issue of *JAMA* demonstrates a proof of principle that deutetrabenazine, compared with placebo, provided improvement in chorea over 12 weeks and allowed less frequent drug dosing with fewer adverse effects. Hopefully, data from the ARC-HD study will support the preliminary findings from this trial and additional research will validate the potential approach of deuterating certain compounds to make safer, longer-lasting drugs.[4]

ARTICLE INFORMATION

Author Affiliations: University of California, San Francisco.

Corresponding Author: Michael Geschwind, MD, PhD, University of California, San Francisco, Neurology, 675 Nelson Rising Lane, Ste 190, San Francisco, CA 94158 (michael.geschwind@ucsf.edu).

Conflict of Interest Disclosures: Both authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Geschwind reports that he has received research grants from National Institute on Aging (R01 AG AG031189), Quest Diagnostics Inc, Tau Consortium, and CurePSP; has served as a consultant for Gerson Lehrman Group, Guidepoint Global, Lundbeck Inc, BestDoctors Inc, MedaCorp, Advanced Medical Inc, Lewis Brisbois Bisgaard & Smith LLP, and NeuroPhage Inc; fees for teaching and writing articles for the American Academy of Neurology; travel support from Teva Pharmaceuticals; speaker fees from Oakstone Publishing Inc; research-related funding through a chaired professorship from the Michael J. Homer Family Fund; and serves on the board of directors for San Francisco Bay Area Physicians for Social Responsibility and on the editorial board of *Dementia & Neuropsychologia*. Dr Paras reported research support from Daiichi-Sankyo, US Department of Defense, and the Tau Consortium.

REFERENCES

1. Huntington Study Group. Effect of deutetrabenazine on chorea among patients with Huntington disease: a randomized clinical trial. *JAMA*. doi:10.1001/jama.2016.8655.

2. Huntington Study Group. Tetrabenazine as antichorea therapy in Huntington disease: a randomized controlled trial. *Neurology*. 2006; 66(3):366-372.

3. Stamler DA, Brown F, Bradbury M. The pharmacokinetics of extended release SD-809, a deuterium-substituted analogue of tetrabenazine [abstract]. *Mov Disord*. 2013;28(suppl 1):765.

4. Gant TG. Using deuterium in drug discovery: leaving the label in the drug. *J Med Chem*. 2014;57(9):3595-3611.

5. Huntington Study Group. Unified Huntington's Disease Rating Scale: reliability and consistency. *Mov Disord*. 1996;11(2):136-142.

6. Roos RA. Huntington's disease: a clinical review. *Orphanet J Rare Dis*. 2010;5:40.

7. Allen IE, Seaman CA. Superiority, equivalence and non-inferiority. *Quality Progress*. February 2007:52-54.

8. Schumi J, Wittes JT. Through the looking glass: understanding non-inferiority. *Trials*. 2011;12:106.

9. Piaggio G, Elbourne DR, Pocock SJ, Evans SJ, Altman DG, Group C; CONSORT Group. Reporting of noninferiority and equivalence randomized trials: extension of the CONSORT 2010 statement. *JAMA*. 2012;308(24):2594-2604.

10. Food and Drug Administration. Guidance for industry non-inferiority clinical trials: draft guidance. Rockville, MD: Office of Communication, Division of Drug Information; 2010:1-66. http://www.fda.gov/downloads/Drugs/.../Guidances/UCM202140.pdf. Accessed June 20, 2016.

11. Huntington Study Group. First-HD ARC-HD. 2016; http://huntingtonstudygroup.org/first-hd-arc-hd. Accessed June 16, 2016.

12. Business Wire. Teva receives complete response letter for NDA for SD-809 for the treatment of chorea associated with Huntington disease [new release]. 2016; http://www.businesswire.com/news/home/20160531005496/en/Teva-Receives-Complete-Response-Letter-NDA-SD-809. Accessed June 16, 2016.

Strategies to Support Surrogate Decision Makers of Patients With Chronic Critical Illness
The Search Continues

Douglas B. White, MD, MAS

Patients with chronic critical illness (defined as a critical illness that requires prolonged mechanical ventilation) are at high risk for death or severe functional impairment.[1] The surrogate decision makers for these patients face challenging decisions about whether to continue life-prolonging treatments given uncertain outcomes. A growing body of research indicates that surrogates often experience symptoms of depression, anxiety, and posttraumatic stress in the months following the intensive care unit (ICU) admission of a family member.[2]

Related article page 51

Moreover, there is concern that many patients receive more life-prolonging treatment than appropriate,[3] in part because surrogates receive inadequate support and information when deliberating about goals of care while patients are in the ICU.[4] Despite the public health importance of patients with chronic critical illness, no validated interventions are available to improve decision making or the psychological outcomes of surrogates.

In this issue of *JAMA*, Carson and colleagues[5] contribute important new knowledge about supporting surrogate decision makers of patients with chronic critical illness. In a multicenter randomized clinical trial that included 365 surrogate decision makers, the investigators assessed whether augmenting the usual support of surrogates with 2 structured conversations delivered by palliative care-trained consultants would decrease psychological distress at 3 months, improve perceptions of communication quality, or decrease end-of-life treatment intensity.

The surrogates in the intervention group received a support and information team intervention that focused on providing emotional support, communicating validated prognostic information about 1-year survival, and discussing the patient's values and preferences. The surrogates in the usual care control group received an informational brochure and family meetings conducted by ICU teams as part of their routine care.

As Carson et al report,[5] there was no difference between study groups for the primary outcome measure of surrogates' symptoms of depression and anxiety 3 months after the patient's hospitalization (Hospital Anxiety and Depression Scale mean scores of 12.2 in the intervention group and 11.4 in the control group). There were also no differences in most secondary outcomes, including surrogates' perceptions of the quality of communication and end-of-life treatment intensity. Surprisingly, the intervention increased surrogates' posttraumatic stress symptoms at 3-month follow-up.

This study has numerous important strengths. The support and information team intervention that was tested is a logical, theory-driven advance over prior ineffective communication interventions in ICUs. For example, the support and information team intervention did not merely provide prognostic information to physicians (as was the strategy in the Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments[6]) but instead ensured that this information was conveyed to family members by highly skilled, empathic physicians. The intervention was pragmatic in design and highly scalable, increasing the chances that if successful it would be readily adopted into practice.

The trial was rigorously conducted. The key elements of the intervention were clearly defined and the study team monitored the fidelity with which the intervention was deployed. The study team achieved a very high rate of long-term follow-up of surrogates, which is difficult to achieve because most family members were either recently bereaved or in the throes of caregiving for a patient with chronic critical illness. The researchers wisely assessed the effects of the intervention on patient outcomes, family outcomes, and