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ORIGINAL RESEARCH

# Effect of Tetrabenazine on Motor Function in Patients with Huntington Disease

Joseph M. Ferrara · Giovanni Mostile · Christine Hunter · Octavian R. Adam · Joseph Jankovic

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## ABSTRACT

***Introduction***: Tetrabenazine (TBZ) reduces chorea related to Huntington disease (HD); however, it is uncertain whether this effect improves functionally relevant motor skills such as hand coordination and balance. The objective of this study was to provide pilot data regarding three motor function tests, which might be useful in monitoring symptom progression and therapeutic response, pending formal validation.

***Methods***: The authors assessed 11 ambulatory patients with HD-related chorea on two occasions: (1) while off TBZ (either prior to starting therapy or following a >24 h washout) and (2) when on a stable dose of TBZ, titrated to optimal effect. Study evaluations included the Jebsen-Taylor Hand Function Test (JTHFT) and Berg Balance Scale, a timed 25-foot walk, the Montreal Cognitive Assessment (MoCA) and the complete United Huntington Disease Rating Scale (UHDRS).

***Results***: Maximal chorea scores (UHDRS item 12) improved from $11.1 \pm 2.9$ to $8.5 \pm 3.9$ while on TBZ ($P = 0.03$), but we could not detect an improvement in functional measures while on TBZ in this small cohort. Scores of the JTHFT were globally slower than published normative data and correlated with MoCA summary scores, but not UHDRS chorea scores.

***Conclusions***: This pilot study did not detect significant functional gains with chorea suppression. The fact that performance on tests of hand function correlates with MoCA but not UHDRS chorea scores highlights the need for additional treatments targeted toward the cognitive aspects of HD.

J. M. Ferrara
Movement Disorder Clinic, Virginia Tech Carilion School of Medicine and Research Institute, Roanoke, VA, USA

G. Mostile · C. Hunter · J. Jankovic (✉)
Department of Neurology, Parkinson Disease Center and Movement Disorders Clinic, Baylor College of Medicine, Houston, TX, USA
e-mail: josephj@bcm.tmc.edu

O. R. Adam
Division of Neurology, Naval Medical Center, Portsmouth, VI, USA

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**Keywords:** Berg Balance Scale; Chorea; Huntington disease; Jebsen-Taylor Hand Function Test; Tetrabenazine

## INTRODUCTION

Huntington disease (HD) is an autosomal dominant, neurodegenerative disorder characterized by cognitive and behavioral dysfunction, as well as various hyper- and hypokinetic movement disorders, of which chorea is generally most prominent. In patients with HD, chorea has a deleterious effect on coordinated limb movements [1, 2], but its effect on overall motor function has not been fully explored.

The pivotal trial that led to the Food and Drug Administration's approval of tetrabenazine (TBZ) for the treatment of chorea associated with HD showed that TBZ significantly reduced chorea scores on the Unified Huntington Disease Rating Scale (UHDRS) [3], but the study could not demonstrate a corresponding improvement in the UHDRS functional assessment measures, including the Total Functional Capacity Scale, Functional Assessment Checklist, and Independence Scale [4]. Indeed, Functional Assessment Checklist scores worsened significantly when compared to controls ($-6.3\%$, $P = 0.02$), and there was a small but significant correlation between these scores and parkinsonism, a potential side effect of TBZ. TBZ also did not appear to lessen falls, although fall rates did diminish in an open-label extension study, which followed the trial [3, 5]. Accordingly, questions remain as to whether and how the antichorea effects of TBZ impact functionally relevant motor skills. The authors, therefore, conducted a pilot study to evaluate tools that may be used to objectively assess the effects of TBZ on hand function and balance.

## MATERIALS AND METHODS

### Participants

Eleven patients with HD (four women, mean age 55 years; Table 1) were recruited from the Baylor College of Medicine Parkinson Disease Center and Movement Disorders Clinic in Houston, TX, USA. The diagnosis of HD was confirmed with genetic testing (CAG repeat length >37 in the *Htt* gene) in either the patient ($n = 9$) or a first-degree relative ($n = 2$). All participants were independently ambulatory and sufficiently disabled by chorea to justify pharmacological intervention. No individuals had used dopamine-receptor blocking drugs within 30 days of enrollment. Antidepressants and benzodiazepines were permitted, but only at stable doses. Additional exclusionary criteria were physical or psychiatric symptoms which might render the patient unsafe to participate in the study as determined by the investigator. All patients signed an informed consent before entering the study approved by Baylor College of Medicine Internal Review Board for Human Research.

### Evaluation Procedures

In this open-label study, all patients were assessed on two occasions within a 6-month period: (1) while off TBZ and (2) when on a stable dose of TBZ, as prescribed by each patient's treating physician (mean cumulative daily dosage $62.5 \pm 19.4$ mg). The "off TBZ" evaluation was performed either prior to starting therapy ($n = 6$) or following a >24 h washout ($n = 5$, mean washout duration

**Table 1** Demographic and nonmotor characteristics of study participants

| | Data are means ± standard deviations [range] and frequencies (percentages) |
|---|---|
| Age at the evaluation | 54.5 ± 13.7 [35–71] |
| Age of symptom onset | 46.1 ± 11.7 [30–65] |
| Female gender | 4 (36.4%) |
| Ethnicity | |
| White, non-Hispanic | 10 (90.9%) |
| Hispanic | 1 (9.1%) |
| Education level (years) | 13.6 ± 4.7 [3–20] |
| Right handedness | 10 (90.9%) |
| Marital status | |
| Married | 6 (54.5%) |
| Divorced | 4 (36.4%) |
| Widowed | 1 (9.1%) |
| CAG repeat length[a] | 43.1 ± 2.5 [40–47] |
| Initial symptoms | |
| Motor | 7 (63.6%) |
| Cognitive | 2 (18.2%) |
| Psychiatric | 2 (18.2%) |
| UHDRS: Cognitive Assessment | |
| Verbal fluency test (raw score) | 15.6 ± 8.1 [6–31] |
| Symbol digit modalities test (raw score) | 17.3 ± 6.6 [7–28] |
| Stroop interference test: color naming (number correct) | 37.5 ± 11.2 [15–50] |
| Stroop interference test: word reading (number correct) | 53.2 ± 13.3 [31–70] |
| Stroop interference test: interference (number correct) | 21.3 ± 8.1 [9–33] |
| UHDRS: Behavioral Assessment[b] | |
| Mood score | 6.8 ± 5.8 [0–16] |
| Behavior score | 4.5 ± 4.2 [0–14] |
| Psychosis score | 0.8 ± 1.9 [0–6] |
| Anxiety/obsessiveness score | 6.7 ± 6.1 [0–16] |
| UHDRS: Functional Assessments[c] | |
| Functional assessment checklist (FAC) | 18.1 ± 5.1 [11–25] |
| Independence scale (IS) | 75.5 ± 10.1 [60–95] |
| Total functional capacity (TFC)[d] | 6.5 ± 3.3 [3–11] |
| MoCA: cumulative score[d] | 19.4 ± 5.4 [7–24] |

*BBS* Berg Balance Scale, *HD* Huntington disease, *JTHFT* Jebsen-Taylor Hand Function Test, *MoCA* Montreal Cognitive Assessment, *T25FW* timed 25-foot walk test, *UHDRS* United Huntington Disease Rating Scale

[a] CAG repeat length data were not available for two patients

[b] Behavioral assessment scores are the sum of frequency and severity scores for corresponding items. For UHDRS scoring, see Reference [3]

[c] The TFC is a 14-unit scale (range 0–13), which rates capacity to hold employment, manage finances, complete domestic chores, perform activities of daily living, and reside independent of nursing care. The FAC is a 25-item checklist, which includes a spectrum of common life activities, such as walking, preparing meals, and driving. Patients are scored either as able (1) or unable (0) to complete each activity without help, and scores are summated. The IS ranges from 10 to 100 units in gradations of 5 units, with 10 representing total bed care requiring enteral nutrition and 100 representing full independence

[d] $n = 10$

34.5 ± 4.5 h). All study instruments were scored as per their published guidelines.

On-off study drug evaluations included the Jebsen-Taylor Hand Function Test (JTHFT) [6],

Berg Balance Scale (BBS) [7], a timed 25-foot walk (T25FW) [8], and the motor section of the UHDRS [4], which was video-recorded and scored by a blinded rater. Before the scored examinations, patients completed a trial run of the JTHFT, BBS, and T25FW to ensure they fully understood and were able to perform the tasks.

In addition to motor testing, patients completed the Montreal Cognitive Assessment (MoCA), a brief but sensitive screening tool for mild cognitive impairment in HD [9]. The authors also administered the cognitive, behavioral, and functional portions of the UHDRS [4]. The UHDRS functional assessment consists of the Total Functional Capacity Scale, Functional Assessment Checklist, and Independence Scale (Table 1). On all UHDRS functional scales, higher scores indicate better functioning than lower scores. The short duration of the study precludes a valid on-off comparison of cognitive, behavioral, and UHDRS functional items. Patients were prospectively monitored for adverse events.

### Data Analysis

Data were expressed as mean ± standard deviation (range) for scalar measures and frequency (percent) for categorical variables. Changes in motor performance on and off TBZ were assessed via parametric *t*-tests and Wilcoxon signed-ranks test for not-normally distributed variables. Pearson's *r* and Spearman's rho were used to assess correlations between the JTHFT and other variables including chorea scores and cognitive parameters.

## RESULTS

Demographic and nonmotor characteristics of the study participants are described in Table 1, and assessments of motor function on and off TBZ are provided in Table 2. Maximal chorea scores (UHDRS item 12) improved from $11.1 \pm 2.9$ to $8.5 \pm 3.9$ while on TBZ ($P = 0.03$). In this small cohort, JTHFT parameters, the BBS, and the T25FW were similar in the on and off TBZ states.

Scores on the JTHFT were globally slower than published normative data [6].

Of 77 JTHFT assessments performed off TBZ for each hand (7 JTHFT items × 11 subjects), only 6.5% of dominant hand and 14.3% of nondominant hand performances were normal, i.e., within the 95% upper confidence limit. Performance on the JTHFT correlated with cognition, specifically the MoCA, but did not correlate with UHDRS maximal chorea scores (Table 3).

Patients reported no adverse effects related to the TBZ washout apart from increased chorea. Chronic use of TBZ was associated with mild fatigue (two patients) and insomnia (one patient).

## DISCUSSION

Tetrabenazine is a benzoquinolizine derivative, which depletes dopamine (and to a lesser extent other biogenic amines) within the central nervous system by reversibly inhibiting presynaptic vesicular monoamine transporter [10]. TBZ has been shown to reduce HD-related chorea in several studies [10–15]. The TETRA-HD [3], a multicenter double-blind placebo-controlled trial, showed that TBZ provided a mean reduction of 23.5% in chorea severity when compared to placebo ($P = 0.0001$), and this effect correlated with benefit in a global measure of clinical outcome. However, it is not clear whether the improvement in chorea score

**Table 2** Evaluation off and on tetrabenazine (TBZ) treatment

| Assessment | Evaluation off TBZ | Evaluation on TBZ | *P* value |
|---|---|---|---|
| UHDRS: Motor | | | |
| Finger taps (item 6a+6b) | 3.2 ± 1.7 | 3.8 ± 1.5 | 0.05 |
| Pronate/supinate hands (item 7a+7b) | 2.7 ± 1.1 | 3.5 ± 1.7 | 0.04 |
| Maximal chorea score (items 12a–g summed) | 11.1 ± 2.9 | 8.5 ± 3.9 | 0.03 |
| Motor cumulative score | 29.8 ± 10.5 | 29.8 ± 11.2 | 1 |
| BBS[a] (cumulative score) | 48.8 ± 6 | 49.8 ± 7.5 | 0.4 |
| T25FW[b] (mean of two trials in seconds) | 5.4 ± 1.9 | 5.3 ± 1.7 | 0.7 |

| JTHFT[c] (s) | Evaluation off TBZ | | Evaluation on TBZ | | *P* value | |
|---|---|---|---|---|---|---|
| | Dominant hand | Nondominant hand | Dominant hand | Nondominant hand | Dominant hand | Nondominant hand |
| Writing[d] | 29.1 ± 15.9 | 75.2 ± 29.6 | 28.4 ± 18.1 | 74.1 ± 29.1 | 0.5 | 0.3 |
| Simulated page turning | 7.6 ± 2.9 | 8.3 ± 3.1 | 6.5 ± 2.5 | 6.9 ± 2 | 0.2 | 0.07 |
| Lifting small, common objects | 10.9 ± 4.7 | 10.7 ± 3.6 | 9.9 ± 2.7 | 11.1 ± 4.7 | 0.4 | 0.9 |
| Simulated feeding | 11.7 ± 3.6 | 16.3 ± 8.4 | 11.8 ± 3.9 | 20.6 ± 23.6 | 0.9 | 0.8 |
| Stacking checkers | 6.8 ± 3.3 | 7.4 ± 3.7 | 5.7 ± 2.1 | 7.3 ± 2.4 | 0.3 | 0.9 |
| Lifting large, light objects | 6.3 ± 1.4 | 7.5 ± 4.6 | 5.4 ± 1.4 | 5.5 ± 1.3 | 0.01 | 0.03 |
| Lifting large, heavy objects | 6.3 ± 2.8 | 7.7 ± 4.2 | 5.5 ± 1.7 | 6.1 ± 1.8 | 0.4 | 0.06 |

Data are means ± standard deviations

*BBS* Berg Balance Scale, *HD* Huntington disease, *JTHFT* Jebsen-Taylor Hand Function Test, *T25FW* timed 25-foot walk test, *UHDRS* United Huntington Disease Rating Scale

[a] The BBS is a 14-item assessment of balance while sitting, standing, transferring, and turning. Each task is graded on an ordinal scale from 0 to 4 and then summed to yield a cumulative score between 0 and 56. Scoring is based on the ability to meet certain time or distance requirements and the capacity to perform items without supervision or assistance. Higher BBS scores reflect better balance

[b] For the T25FW, subjects were directed to one end of a defined course and instructed to walk to the opposite side in a straight line as quickly as possible without compromising safety. A 25-foot mid-course section was timed on two occasions and the times were averaged

[c] The JTHFT is a seven-item test, which is widely used to assess a broad range of common hand functions. Participants are timed while performing writing, simulated page turning (card flipping), picking up small objects (e.g., coins and paperclips), simulated feeding, stacking checkers, and moving empty and weighted aluminum cans. Higher JTHFT scores reflect slower task completion and worse manual function. Normative scores are available for different age and gender groups [6]

[d] For the nondominant hand, 5 patients had a maximal score of 99 s as they were not able to complete the task

**Table 3** Correlation between items of the JTHFT and the MoCA summary score

| JTHFT | MoCA total score | |
|---|---|---|
| | Dominant hand | Nondominant hand |
| Writing | −0.852 (0.002) | −0.432 (0.2) |
| Simulated page turning | −0.888 (0.001) | −0.799 (0.006) |
| Lifting small, common objects | −0.661 (0.04) | −0.764 (0.01) |
| Simulated feeding | −0.545 (0.1) | −0.669 (0.03) |
| Stacking checkers | −0.824 (0.003) | −0.678 (0.03) |
| Lifting large, light objects | −0.837 (0.003) | −0.873 (0.001) |
| Lifting large, heavy objects | −0.827 (0.003) | −0.706 (0.02) |

Data are correlation coefficients (*P* values)
Evaluations performed off TBZ, $n = 10$
*JTHFT* Jebsen-Taylor Hand Function Test, *MoCA* Montreal Cognitive Assessment

translates into improvement in overall motor function.

Prior studies of HD have primarily utilized the UHDRS to assess patient functional parameters; specifically the Total Functional Capacity Scale, Functional Assessment Checklist, and Independence Scale. The functional assessment portion of the UHDRS has merits: it is easily administered, validated [4], closely linked with health-related quality of life [16], and able to predict the rate of future decline [17]. The UHDRS functional assessments, however, contain several elements that are cognitively demanding; for example, patients are rated on their ability to maintain employment, drive, manage finances, supervise children, and administer medications. These items are relevant to HD, but they are unlikely to illuminate any potential benefits in function that arise from treating motor symptoms including chorea. Other items within the UHDRS functional battery are less complex and perhaps more apt to improve with suppression of chorea (e.g., dressing and eating); however, the UHDRS appraises these tasks in a manner that is insensitive to change. Therefore, it is not surprising that pharmacotherapies targeted toward chorea, including TBZ, do not positively influence the UHDRS functional assessments [3, 5, 17, 18] and that progressive decline in these domains is predicted predominantly by cognitive and behavioral parameters [17, 19]. Given these limitations, the authors explored the effect of TBZ on motor function using the JTHFT, BBS, and T25FW, three instruments in which patients are assessed while performing motor tasks.

In this pilot study, TBZ had little impact on the time needed to complete tests of hand function, and both walking speed and balance were unchanged by treatment. The antichorea effect of TBZ seen in the present study was less than that found in the only large-scale, placebo-controlled trial of the drug [3]. It is unknown whether more robust control of chorea through higher dosing would have yielded better performance on the motor function tests that were studied in the present study. The fact that motor performance on the JTHFT correlated with cognitive dysfunction but not chorea severity suggests that factors apart from chorea

have a substantial impact on motor tasks. Pertinent impairments might include attention deficits and other deficiencies in executive function [20, 21] as well as impairments in the ability to automatize behavior [22].

The authors recognize the methodological limitations of the present study, including its small sample size and open-label design. Although a placebo-controlled study would be preferable, the effect of placebo on the motor features of HD is modest [23]. The use of a drug washout to assess motor status off TBZ also introduces potential problems, as withdrawal of a therapy may not approximate a treatment naive state; however, TBZ has a short half-life, which makes a washout design feasible. In animal studies, the drug is essentially eliminated from the brain within 24 h of withdrawal [24], and prior studies of patients with HD have shown that chorea re-emerges within a mean of 5 h following withdrawal [12]. The pharmacodynamic changes that follow chronic administration of TBZ are not known; however, TBZ washout does not appear to intensify chorea beyond pretreatment levels, and withdrawal is generally well-tolerated [3, 5, 14]. Phenotypic variability in HD also poses challenges, as gains in motor function from chorea suppression may be offset by worsening bradykinesia and dystonia in some patients.

In conclusion, improved therapies for HD must address clinically relevant endpoints, including motor function. The present study provides pilot data regarding three motor function tests, which might be useful in monitoring symptom progression and therapeutic response, pending formal validation. The fact that performance on tests of hand function correlates with MoCA, but not UHDRS chorea scores, highlights the need for additional treatments targeted toward the cognitive aspects of HD.

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***Conflict of interest.*** Drs. Adam, Ferrara, Hunter, and Mostile have nothing to disclose. Dr. Jankovic has received personal compensation for activities with Lundbeck, Inc.



## REFERENCES

1. Fenney A, Jog MS, Duval C. Bradykinesia is not a "systematic" feature of adult-onset Huntington's disease; implications for basal ganglia pathophysiology. Brain Res. 2008;1193:67–75.

2. Reilmann R, Kirsten F, Quinn L, Henningsen H, Marder K, Gordon AM. Objective assessment of progression in Huntington's disease: a 3-year follow-up study. Neurology. 2001;57:920–4.

3. Huntington Study Group. Tetrabenazine as antichorea therapy in Huntington disease: a randomized controlled trial. Neurology. 2006;66:366–72.

4. Huntington Study Group. Unified Huntington's Disease Rating Scale: reliability and consistency. Mov Disord. 1996;11:136–42.

5. Frank S. Tetrabenazine as anti-chorea therapy in Huntington disease: an open-label continuation

study. Huntington Study Group/TETRA-HD Investigators. BMC Neurol. 2009;9:62.

6. Jebsen RH, Taylor N, Trieschmann RB, Trotter MJ, Howard LA. An objective and standardized test of hand function. Arch Phys Med Rehabil. 1969;50:311–9.

7. Berg KO, Maki BE, Williams JI, Holliday PJ, Wood-Dauphinee SL. Clinical and laboratory measures of postural balance in an elderly population. Arch Phys Med Rehabil. 1992;73:1073–80.

8. Lynch DR, Farmer JM, Wilson RL, Balcer LJ. Performance measures in Friedreich ataxia: potential utility as clinical outcome tools. Mov Disord. 2005;20:777–82.

9. Videnovic A, Bernard B, Fan W, Jaglin J, Leurgans S, Shannon KM. The Montreal Cognitive Assessment as a screening tool for cognitive dysfunction in Huntington's disease. Mov Disord. 2010;25:401–4.

10. Kenney C, Jankovic J. Tetrabenazine in the treatment of hyperkinetic movement disorders. Expert Rev Neurother. 2006;6:7–17.

11. Ondo WG, Tintner R, Thomas M, Jankovic J. Tetrabenazine treatment for Huntington's disease-associated chorea. Clin Neuropharmacol. 2002;25:300–2.

12. Kenney C, Hunter C, Davidson A, Jankovic J. Short-term effects of tetrabenazine on chorea associated with Huntington's disease. Mov Disord. 2007;22:10–3.

13. Adam OR, Jankovic J. Symptomatic treatment of Huntington disease. Neurotherapeutics. 2008;5:181–97.

14. Frank S, Ondo W, Fahn S, et al. A study of chorea after tetrabenazine withdrawal in patients with Huntington disease. Clin Neuropharmacol. 2008;31:127–33.

15. Jankovic J. Treatment of hyperkinetic movement disorders. Lancet Neurol. 2009;8:844–56.

16. Ho AK, Gilbert AS, Mason SL, Goodman AO, Barker RA. Health-related quality of life in Huntington's disease: which factors matter most? Mov Disord. 2009;24:574–8.

17. Marder K, Zhao H, Myers RH, et al. Rate of functional decline in Huntington's disease. Huntington Study Group. Neurology. 2000;54:452–8.

18. Feigin A, Kieburtz K, Bordwell K, et al. Functional decline in Huntington's disease. Mov Disord. 1995;10:211–4.

19. Hamilton JM, Salmon DP, Corey-Bloom J, et al. Behavioural abnormalities contribute to functional decline in Huntington's disease. J Neurol Neurosurg Psychiatry. 2003;74:120–2.

20. Delval A, Krystkowiak P, Delliaux M, et al. Role of attentional resources on gait performance in Huntington's disease. Mov Disord. 2008;23:684–9.

21. Rodrigues GR, Souza CP, Cetlin RS, et al. Use of the frontal assessment battery in evaluating executive dysfunction in patients with Huntington's disease. J Neurol. 2009;256:1809–15.

22. Thompson JC, Poliakoff E, Sollom AC, Howard E, Craufurd D, Snowden JS. Automaticity and attention in Huntington's disease: when two hands are not better than one. Neuropsychologia. 2010;48:171–8.

23. Cubo E, González M, Del Puerto I, FernándezArconada O, Garcia de Yebenes J. Impact of placebo treatment in Huntington's disease: P05.025. Neurology. 2010;74(Suppl. 2):A413.

24. Quinn GP, Shore PA, Brodie BB. Biochemical and pharmacological studies of RO 1–9569 (tetrabenazine), a nonindole tranquilizing agent with reserpine-like effects. J Pharmacol Exp Ther. 1959;127:103–9.