Evidence-based guideline: Pharmacologic treatment of chorea in Huntington disease


ABSTRACT

Objective: To develop an evidence-based guideline assessing pharmacologic options for treating Huntington disease (HD) chorea.

Methods: We evaluated available evidence from a structured literature review performed through February 2011.

Results and recommendations: If HD chorea requires treatment, clinicians should prescribe tetrabenazine (up to 100 mg/day), amantadine (300–400 mg/day), or riluzole (200 mg/day) (Level B) for varying degrees of expected benefit. Occurrence of adverse events should be discussed and monitored, particularly depression/suicidality and parkinsonism with tetrabenazine and elevated liver enzymes with riluzole. Clinicians may also prescribe nabibline for modest decreases (1- to <2-point changes on the Unified Huntington's Disease Rating Scale [UHDRS] chorea score) in HD chorea (Level C), but information is insufficient to recommend long-term use, particularly given abuse potential concerns (Level U). Clinicians should not prescribe riluzole 100 mg/day for moderate (2- to <3-point UHDRS chorea change) short-term benefits (Level B) or for any long-term (3-year) HD antichoreic goals (Level B). Clinicians may choose not to prescribe ethyl-EPA (Level B), minocycline (Level B), or creatine (Level C) for very important improvements (>3-point UHDRS chorea change) in HD chorea. Clinicians may choose not to prescribe coenzyme Q10 (Level B) for moderate improvements in HD chorea. Data are insufficient to make recommendations regarding the use of neuroleptics or donepezil for HD chorea treatment (Level U). Neurology® 2012;79:597-603

Glossary

AAN = American Academy of Neurology; AE = adverse event; CI = confidence interval; ethyl-EPA = ethyl-eicosapentaenoic acid; FDA = Food and Drug Administration; HAM-D = Hamilton Depression Scale; HD = Huntington disease; HSG = Huntington Study Group; NMS = neuropsychiatric malignant syndrome; OR = odds ratio; RCT = randomized controlled trial; SAE = serious adverse event; TBZ = tetrabenazine; TFC = total functional capacity; TMS-4 = Total Motor Score 4 subscale of the Unified Huntington’s Disease Rating Scale; UHDRS = Unified Huntington’s Disease Rating Scale.

Chorea is a hallmark of Huntington disease (HD) along with cognitive decline and psychiatric impairment. It often develops early, gradually worsening and plateauing in late stages.2 Motor dysfunction, including chorea, decreases functional capacity, particularly in early HD.2–4 Chorea worsens weight loss5 and can compromise safety,6 including increasing fall risk.7 Treating chorea is an important part of HD management.

The pathophysiology and neurochemical bases of HD are complex and incompletely understood. Dopamine and glutamate transmission and interactions are affected, contributing to striatal and cortical vulnerability and to features such as chorea.8 Most agents investigated for HD chorea target these neurotransmitters and receptors. Neuroprotective trials often focus on agents that may prevent oxidative stress or glutamatergic changes related to excitotoxic stress.9

For this evidence-based guideline, we asked the following question: For adult patients with HD requiring symptomatic chorea therapy, what available...
pharmacologic agents effectively reduce chorea as measured by validated scales?

**DESCRIPTION OF THE ANALYTIC PROCESS**

MEDLINE and EMBASE searches through February 2011 performed in all languages (see appendix e-1 on the Neurology® Web site at www.neurology.org for strategy) identified 424 citations. Both authors reviewed titles and abstracts for relevance and rated the resulting 33 articles using the American Academy of Neurology criteria for therapeutic classification (appendix e-4). Results of the article abstraction are presented in table e-1. Recommendations were linked to strength of evidence (appendix e-5). Disagreements were resolved by discussion and consensus.

Inclusion criteria were as follows: subjects with genetically confirmed HD or HD clinical features plus confirmed family history, a comparison group, an available pharmacologic intervention, measurement of chorea change using a validated outcome measure, and ≥20 patients. Studies with primary neuroprotective or tolerability endpoints were included if chorea was a secondary endpoint.

Although the Unified Huntington’s Disease Rating Scale (UHDRS)10 is the main outcome measure for HD studies, clinically important change on the UHDRS remains undefined. The 106-point UHDRS motor scale measures chorea, parkinsonism, dystonia, eye movements, and other signs. The 28-point maximal chorea subscore rates facial, bucco-oral-lingual, trunk, and extremity chorea.10 In early HD, a 1-point UHDRS total motor score increase is associated with an approximate 10% loss in likelihood of being able to work, manage finances, drive, and supervise children.3 The influence of different motor features was not reported. Thus, for the purposes of this guideline we considered <1-point decrease in the UHDRS total motor subscore unimportant, 1- to <2-point decrease modestly important, 2- to <3-point decrease moderately important, and ≥3-point decrease very important.

When antichorea medication is initiated, long-term therapy is typically expected given HD’s progressive nature, but there may be occasions when short-term chorea reductions are desired (e.g., patient undergoing imaging studies or procedures or attending important events). For this guideline, short- and long-term study durations were considered separately because of differing outcomes or adverse events (AEs). Studies conducted over ≤12 months were considered short-term; studies lasting >12 months, long-term.

AEs are included in the text for pharmacotherapies where evidence supports Level A–C recommendations for use. AEs for therapies with evidence against use or with insufficient evidence are shown in table e-2. Serious adverse event (SAE) information is included from trials and Micromedex 2.0 (accessed July 15, 2011).

**ANALYSIS OF EVIDENCE**

Dopamine-modifying drugs. Tetrabenazine. Two studies examined tetrabenazine (TBZ), a vesicular monoamine transporter inhibitor depleting dopamine and other central monoamines, for chorea. A 12-week, 84-subject Class I randomized controlled trial (RCT) of TBZ (titrated to 100 mg daily over 7 weeks) found significant improvement in UHDRS total maximal chorea scores from baseline to an average of weeks 9 and 12 in the TBZ group (−5.0 ± 0.5) vs the placebo group (−1.5 ± 0.7) (p = 0.0001, effect difference −3.5, 95% confidence interval [CI] −3.8 to −3.2).11 The adjusted odds ratio (OR) for chorea severity decrease of ≥3 UHDRS units was 9.9 (95% CI 3.2 to 29.9, p < 0.0001). TBZ was also superior on the 7-point Clinical Global Impression (CGI) Global Improvement Scale (adjusted effect size −0.7 CGI units [95% CI −1.3 to −0.2]). When TBZ was discontinued at study completion, chorea worsened in patients receiving TBZ in comparison with those receiving placebo (adjusted effect size 4.4 UHDRS units, p < 0.0001).11

An RCT of TBZ withdrawal (Class II)3 in 30 TBZ-treated patients with HD randomized to continue or discontinue TBZ on day 1 or 3 (using placebo for blinding) found the day 3 UHDRS chorea score increased by 5.3 units in the early-discontinuation group as compared with the other groups combined (p = 0.0773). Post hoc analysis of the linear trend following TBZ discontinuation was positive for reemergent chorea (p = 0.0486),12 but a withdrawal effect (rather than prior antichoreic efficacy) could not be excluded.

**Adverse events.** TBZ-related AEs are concerning, as 2 known AEs—depression and parkinsonism—also occur in HD. Patients with HD have higher risks of suicidal ideation and completion than the general population.13 Information regarding TBZ AEs in HD comes from the treatment RCT and a Class IV open-label continuation study where 45 subjects completed 80 weeks of treatment (up to 200 mg/day). In the RCT, AEs were more common in TBZ-treated patients (91% vs 70% of placebo-treated patients, p = 0.01), but all between-group differences resolved by maintenance phase conclusion. In the continuation study, insomnia, somnolence, and diarrhea occurred during TBZ titration but resolved during maintenance.14 Common treatment-emergent AEs in the continuation study included...
sedation/somnolence (24%), depressed mood (23%), anxiety (17%), and insomnia (13%). SAES of concern included suicide (1 in each study), falls (1 in the RCT and 2 in the continuation study), and extreme restlessness (1 in each study).11,14

No subject had posttreatment depression according to Hamilton Depression Scale (HAM-D) scores in either study, and no subject had baseline depression.11,14 Twenty-three percent of subjects in the continuation study reported depressed mood.14

In the RCT, UHDRS parkinsonism scores did not differ between groups. Patients receiving TBZ worsened on UHDRS Functional Checklist scores (+0.8 units vs −0.4 units in placebo-treated patients, p = 0.02), which had small but significant correlations with worsening UHDRS parkinsonism (γ = 0.24, p = 0.027) and HAM-D scores (γ = 0.30, p = 0.006). Despite slight worsening on the UHDRS Functional Checklist with TBZ, there was no difference between groups on the Functional Impact Scale, and the TBZ group improved significantly on the CGI, leaving interpretation of disability findings unclear.11 In the continuation study, significant worsening occurred between baseline and week 80 on UHDRS parkinsonism scores (2.1 ± 4.3, p = 0.002) and Unified Parkinson’s Disease Rating Scale dysarthria scores (0.4 ± 0.8, p < 0.002), but the worsening was consistent with disease progression.14

TBZ can cause prolonged QT interval and neuroleptic malignant syndrome (NMS) (Micromedex 2.0), but neither has been reported in HD studies.11

Conclusion. Based on 2 studies (1 Class I, 1 Class II), TBZ is likely effective in decreasing HD chorea to a very important degree. AEs should be monitored.

Clozapine. One RCT examined the atypical antipsychotic clozapine (with dose increases on alternating days up to 150 mg/day) vs placebo in 33 patients with HD.15 The study was rated Class III because of poor documentation of randomization/concealment, lack of a prespecified primary outcome, group baseline differences, and exclusion of subjects from final analysis. Among the 26 study-completers, 18 neuroleptic-naïve patients treated with clozapine had greater reduction in mean difference (SD) on the Abnormal Involuntary Movement Scale vs placebo-treated patients (−7.3 [3.4] vs 0 [4.8], p = 0.02). Videotape ratings and mean UHDRS chorea score differences (−4.0 [3.0] vs −0.3 [3.7], p = 0.07) did not differ between groups. Chorea reduction was associated with reduced self-evaluated disability (p = 0.02) but not partner-evaluated disability (p = 0.78). Eight patients already taking neuroleptics did not benefit from clozapine, but small sample size precluded determining efficacy.15 AEs were common and sometimes serious (table e-2).15

Glutamatergic-modifying drugs. Amantadine. Two randomized crossover trials studied oral amantadine, an NMDA receptor antagonist, vs placebo in 2-week crossover blocks. A Class I study examined amantadine 300 mg daily in 24 subjects using blinded video assessment and a 24-point chorea scale validated within the study (for which the same assumptions were made regarding possible clinically important differences as for the UHDRS). The mean chorea score at baseline was 9.6 (SD 3.1); mean scores after amantadine and placebo treatments were 9.6 (3.7) and 9.3 (3.2), respectively. The difference was non-significant, but the 95% CI of the effect difference was −1.4 to 1.0. Nineteen subjects using amantadine reported improved chorea as opposed to only 6 subjects using placebo (p = 0.006). Mean quality of life scores improved after amantadine treatment (3.9 ± 0.7) vs placebo (2.95 ± 0.7, p < 0.001).16

A Class II study found maximal UHDRS chorea scores decreased by 18% in 24 patients receiving amantadine (increased over 4 days to 400 mg daily) vs 5% for placebo (p = 0.0007). Absolute reductions were not reported. Antichoreic effects varied widely.17

Adverse events. Possible amantadine-related AEs included hallucinations or confusion, increased forgetfulness, agitation/anxiety, exacerbation of morbid thoughts, diarrhea, nausea, and sleepiness.16,17 Potential amantadine SAEs (not reported in these studies) include cardiovascular effects, agranulocytosis and other hematologic events, hypersensitivity reactions, NMS, suicidal intent, acute respiratory failure, and pulmonary edema (Micromedex 2.0).

Conclusion. Whereas video ratings showed no difference in chorea scores between amantadine and placebo (1 Class I study), a modest amantadine effect on HD chorea could not be excluded. Furthermore, blinded patient-reported outcomes described a beneficial effect of amantadine (1 Class I study), and a Class II study suggested amantadine is likely effective in decreasing HD chorea (degree unknown).

Riluzole. Riluzole has antiglutamatergic and anti-excitotoxic properties. Two Class I RCTs studied riluzole using different doses (100 mg or 200 mg) and durations (8 weeks and 3 years). The first RCT measured UHDRS chorea scores in 63 patients receiving riluzole 100 mg or 200 mg or placebo divided into twice-daily dosing for 8 weeks (1 dose-titration week).18 Total maximal chorea was significantly reduced in patients receiving riluzole 200 mg/day.
(−2.2 ± 3.3, p = 0.01) but not 100 mg/day (−0.2 ± 2.9) vs placebo (+0.7 ± 3.4). The effect difference between riluzole 100 mg/day and placebo was 0.9 (95% CI −1.1 to 2.9). Post hoc censoring of 10 patients taking concomitant neuroleptics showed no benefit of riluzole 200 mg/day, but scores were not provided. Riluzole did not improve the UHDRS functional checklist or total functional capacity (TFC).18

The second RCT (n = 537) found no significant difference in UHDRS chorea scores at 3 years in subjects treated with riluzole 50 mg twice daily (+3.7) or placebo (+3.2) (effect difference 0.5, 95% CI −0.33 to 1.33).19 However, 14.4% (26/180) of placebo-treated subjects withdrew to start antichoreic medication vs 9.0% (32/357) of riluzole-treated subjects (p < 0.0001).19

Adverse events. Elevated liver enzymes were more common with riluzole.18,19 Six deaths occurred in 537 subjects in the 3-year study; 5 were suicides (2 in placebo subjects, 3 in riluzole subjects). Two placebo-treated and 4 riluzole-treated patients unsuccessfully attempted suicide.19 The studies did not report other potential riluzole SAEs (cardiac arrest, neutropenia, hepatitis, jaundice, extrinsic allergic alveolitis, interstitial lung disease) (Micromedex 2.0).

Conclusion. Riluzole conclusions vary by dose and treatment duration. Based on 1 Class I RCT, riluzole 200 mg/day likely moderately decreases HD chorea at 8 weeks. Riluzole 100 mg/day likely has no moderate antichoreic benefit at 8 weeks, but a modest benefit cannot be excluded (1 Class I RCT). Riluzole 100 mg/day likely fails to improve chorea at 3 years (1 Class I RCT).

Energy metabolites. Ethyl-EPA. Two RCTs compared 1 mg BID of ethyl-eicosapentaenoic acid (ethyl-EPA), an ω-3 fatty acid, with placebo. Ethyl-EPA’s mechanism of effect in HD is unknown. A placebo-controlled Class II RCT with 135 subjects found that 12 months of ethyl-EPA treatment did not improve Total Motor Score 4 subscale (TMS-4) scores or chorea in the intention-to-treat group (estimated chorea effect difference 0.47, 95% CI −2.03 to 1.09, p = 0.551).20 In the per-protocol analysis, TMS-4 scores were better with ethyl-EPA (p = 0.046), partially because of improved UHDRS chorea scores (p = 0.038).

In TRENTHD21 (Class I), investigators randomized 316 patients to ethyl-EPA vs placebo for 6 months. Total chorea scores were not significantly different (−0.9 with ethyl-EPA vs −0.4 with placebo, p = 0.20), but data were insufficient to calculate CIs. Ethyl-EPA was generally well tolerated (table e-2).20,21

Conclusion. Based on 1 Class I study and 1 Class II study, ethyl-EPA is likely ineffective for treating HD chorea. However, the Class II study lacked statistical precision to exclude a moderate antichoreic benefit, and published data from the Class I study were insufficient to calculate CIs for the effect difference.

Creatine. Creatine is a high-energy phosphate donor studied in HD for theorized oxidative stress reduction.22 One Class II RCT randomizing 64 patients to receive creatine 8 mg/day or placebo found no difference in any 16-week UHDRS outcome, including total chorea (+2.0 with creatine vs −0.3 with placebo).22 Data were insufficient to calculate the 95% CI of the effect difference. The difference in means at week 16 was 0.4 (95% CI −2.5 to 3.0).

Conclusion. Creatine is possibly ineffective in improving HD chorea to a very important extent (1 Class II study), but lack of statistical precision suggests moderate benefit cannot be excluded.

Other. Donepezil. Donepezil is an acetylcholinesterase inhibitor studied because cholinergic system damage may cause some HD symptoms.23 One RCT (Class I) compared donepezil (5 mg daily for 6 weeks, then 10 mg daily for 6 weeks) with placebo in 30 subjects.23 Median change in UHDRS chorea scores was not different between groups (0.5 with donepezil, −1.5 with placebo; p = 0.32). Data were insufficient to calculate CIs.

Conclusion. One Class I RCT had insufficient precision to support or refute donepezil efficacy for HD chorea.

Coenzyme Q10. A single RCT (Class I) randomized 347 patients to remacemide (which is not commercially available), coenzyme Q10 300 mg BID, both remacemide and coenzyme Q10, or placebo for 30 months.24 Coenzyme Q10 was associated with a trend toward a smaller decline in TFC at 30 months; however, chorea did not improve (adjusted coenzyme Q10 effect −0.10 units, 95% CI −1.05 to 0.86).

Conclusion. Coenzyme Q10 is likely ineffective in moderately improving HD chorea (1 Class I study), but modest benefit cannot be excluded.

Minocycline. Minocycline is an antibiotic with anti-inflammatory and antiapoptotic properties studied in HD on the basis of preclinical evidence.25 One Class I RCT studied minocycline tolerability in 60 patients with HD.25 Mean change (SD) in UHDRS chorea scores was 0.32 (3.67) in the 200-mg/day group, −0.44 (3.26) in the 100-mg/day group, and 0.43 (2.83) in the placebo group (p = 0.57).25 The effect size was −0.87 (95% CI −2.77 to 1.03) for minocycline 100 mg/day and −0.11 (95% CI −2.13 to 1.91) for 200 mg/day.
Conclusion. Minocycline is likely ineffective in improving HD chorea to a very important extent (1 Class I study), but lack of statistical precision suggests moderate benefit cannot be excluded.

Nabilone. A Class II study of nabilone, a synthetic cannabinoid, randomized 22 subjects to 5-week crossover blocks of nabilone (1 or 2 mg) or placebo. Nabilone decreased UHDRS chorea scores by 1.68 (95% CI 0.44 to 2.92, p = 0.009). The study was insufficiently powered to detect dose differences. Cannabinoids may work by decreasing glutamate release or modulating other neurotransmitters via basal ganglia cannabinoid receptors.

Adverse events. One nabilone subject reported severe sedation. Drowsiness and forgetfulness were the most frequent AEs. AE and dropout rates were similar between groups. “Psychotic disorder” is the only described nabilone SAE (Micromedex 2.0), but no increase in psychosis occurred in the trial. Nabilone is listed by the US Food and Drug Administration (FDA) as a class 2 controlled substance with high abuse potential.

Conclusion. Based on 1 Class II RCT, nabilone possibly modestly improves HD chorea. Effects of long-term treatment, including safety and addiction potential, are unknown.

CLINICAL CONTEXT TBZ is the only FDA-approved drug for treating HD chorea, and thus other drug options are off-label. HD studies typically enroll patients who are ambulatory, retain good functional capacity, and are free from disabling depression or cognitive decline. Thus, study results may not apply to the entire HD population. Additionally, the clinically meaningful change for UHDRS chorea is not established. We ranked degree of benefit using the clinically meaningful change for UHDRS chorea.2 The study was insufficiently powered to detect dose differences. It is possible that 200 mg/day is the minimum dose needed for antichoreic effect. There is insufficient evidence to conclude whether patients unable to tolerate 200 mg/day should continue riluzole.

Neuroleptic agents are traditionally used for HD chorea treatment, and neuroleptics and antidepressants are the most commonly prescribed drugs in HD. Other than the clozapine study, only 2 studies of neuroleptic treatment for HD chorea had sufficient sample size for consideration. Both examined tiapride, an atypical neuroleptic unavailable in North America, but neither used validated outcome measures. Neuroleptic agents may be reasonable options given behavioral concerns in HD and historical suggestion of antichoreic benefit, but formal guidelines cannot be provided. Additionally, neuroleptic AEs require consideration, particularly parkinsonism.

Given prevalence of depression and suicide in HD, clinicians should screen for these before and during TBZ use, and should monitor for signs of parkinsonism. EKG changes were not observed in HD TBZ studies, but pretreatment EKGs are reasonable. US TBZ prescribing information recommends genotyping for CYP2D6, the enzyme responsible for metabolizing TBZ, prior to TBZ use. Whether this advice is followed clinically is unknown. Possible interactions with other medications metabolized by the CYP2D6 system, such as fluoxetine or paroxetine, should be considered during TBZ dosing.

The significance of conflicting findings for different doses and treatment durations of riluzole is unknown. It is possible that 200 mg/day is the minimum dose needed for antichoreic effect. There is insufficient evidence to conclude whether patients unable to tolerate 200 mg/day should continue riluzole at the 100-mg dose.

RECOMMENDATIONS
1. If HD chorea requires treatment, clinicians should prescribe TBZ (up to 100 mg/day), amantadine (300–400 mg/day), or riluzole (200 mg/day) (Level B). TBZ likely has very important antichoreic benefits, and riluzole 200 mg/day likely has moderate benefits (Level B). The degree of benefit for amantadine is unknown. Clinicians should discuss possible AEs with patients with HD and monitor for their occurrence, particularly parkinsonism and depression/suicidality with TBZ and elevated liver enzymes with riluzole.

2. Clinicians may prescribe nabilone for modest decreases in HD chorea (Level C), but information is insufficient to recommend long-term use, particularly given abuse potential concerns (Level U).

3. Whereas riluzole 200 mg/day likely decreases chorea, clinicians should not prescribe riluzole.
100 mg/day for moderate short-term benefits (Level B) or for any long-term (3-year) HD antichoreic goals (Level B). Modest short-term benefits of riluzole 100 mg/day cannot be excluded.

4. Clinicians may choose not to prescribe ethyl-EPA (Level B), minocycline (Level B), or creatine (Level C) for very important improvements in HD chorea. Moderate antichoreic benefits cannot be excluded.

5. Clinicians may choose not to prescribe coenzyme Q10 (Level B) for moderate improvements in HD chorea. Modest antichoreic benefits cannot be excluded.

6. Data are insufficient to make recommendations regarding use of clozapine, other neuroleptics, or donepezil for HD chorea treatment (Level U).

RECOMMENDATIONS FOR FUTURE RESEARCH

1. HD remains a devastating neurodegenerative disease in need of neuroprotective and symptomatic treatments; research in both treatment areas is warranted.

2. The minimal clinically important difference for UHDRS scores should be determined.

3. High-quality studies evaluating the antichoreic efficacy of neuroleptic agents should be performed given these agents’ common clinical use for this indication.

4. Adequate sample size to detect changes in outcome measures is critical.

5. Quality of life data across chorea severities should be sought to guide research and clinical decisions regarding treatment.

AUTHOR CONTRIBUTIONS

M. Armstrong: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, acquisition of data, statistical analysis, study supervision. J. Miyasaki: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, statistical analysis.

DISCLOSURE

M. Armstrong received support as an Edmond J. Safra fellow at Toronto Western Hospital while working on this project, serves as a member of the AAN Guideline Development Subcommittee and as a Level of Evidence reviewer for Neurology®; and receives research funding from Abbott as a study sub-investigator. J. Miyasaki received grants from Medivation, NIH, and Michael J Fox Foundation; consultancy fees from Novartis for Data study subinvestigator. J. Miyasaki received grants from Medivation, NIH, and the physician caring for the patient, based on all circumstances involved. The clinical context section is made available in order to place the evidence-based guideline(s) into perspective with current practice habits and challenges. No formal practice recommendations should be inferred.

CONFLICT OF INTEREST

The American Academy of Neurology is committed to producing independent, critical and truthful clinical practice guidelines (CPGs). Significant efforts are made to minimize the potential for conflicts of interest to influence the recommendations of this CPG. To the extent possible, the AAN keeps separate those who have a financial stake in the success or failure of the products appraised in the CPGs and the developers of the guidelines. Conflict of interest forms were obtained from all authors and reviewed by an oversight committee prior to project initiation. AAN limits the participation of authors with substantial conflicts of interest. The AAN forbids commercial participation in, or funding of, guideline projects. Drafts of the guideline have been reviewed by at least 3 AAN committees, a network of neurologists, Neurology peer reviewers, and representatives from related fields. The AAN Guideline Author Conflict of Interest Policy can be viewed at www.aan.com.

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