

Huntington's Disease: EMERGING CONCEPTS IN DIAGNOSIS AND TREATMENT

ADAM ROSENBLATT, MD

Co-director, Huntington Disease Program
VCU Parkinson's and Movement Disorders Center
Virginia Commonwealth University
Richmond, Virginia

SAMUEL FRANK, MD

Associate Professor of Neurology
Boston University School of Medicine
Boston, Massachusetts

SUPPLEMENT TO

NEUROLOGY
REVIEWS®



This supplement is sponsored by Raptor Pharmaceuticals Inc.



Huntington's Disease:

EMERGING CONCEPTS IN DIAGNOSIS AND TREATMENT

ADAM ROSENBLATT, MD

Co-director, Huntington Disease Program
VCU Parkinson's and Movement Disorders Center
Virginia Commonwealth University
Richmond, Virginia

SAMUEL FRANK, MD

Associate Professor of Neurology
Boston University School of Medicine
Boston, Massachusetts

INTRODUCTION

Huntington's disease (HD) is an inherited autosomal-dominant neurodegenerative disorder caused by a single mutation in the *Huntingtin (HTT)* gene on chromosome number 4.¹ Huntington's disease is progressive and fatal. The disease typically develops in middle age but has the potential to affect people from childhood to older age.² Offspring of patients with HD have a 50/50 chance of inheriting the mutation. The incidence of HD has been estimated as 1 per 100,000 in western societies and up to 5-10 per 100,000 worldwide.^{3,4}

The mutant form of *HTT* has an elongated polyglutamine sequence of cytosine-adenine-guanine (CAG) that is toxic to brain cells.¹ The number of CAG repeats is associated with age at onset. Patients with earlier age at onset often have more severe disease due to more symptoms of dystonia, dysphagia, and gait issues. Twenty-six or fewer CAG repeats are considered normal and individuals with 27 to 34 CAG repeats may have subtle abnormalities suggestive of an endophenotype. Patients with 35 to 39 CAG repeats have reduced penetrance. The threshold for 100% penetrance is ≥ 40 CAG repeats and is usually associated with disease expression; the age of HD onset is inversely

correlated with the number repeats above that threshold.⁵ Thus, a patient with 70 or 80 repeats may present with HD during childhood while a patient with 40 repeats may not present until he or she is older.¹

PATHOPHYSIOLOGY

Early pathogenesis of HD includes misfolding of *HTT* to a β -sheet structure and post-translational alterations (eg, cleavage, altered phosphorylation).¹ The mutant huntingtin protein can alter gene transcription, affect cellular metabolism (ie, mitochondrial function), and cause abnormalities in cellular proteostasis mechanisms.¹ Huntington's disease causes degeneration of the brain, eventually globally, but it particularly affects the basal ganglia early in the course of disease, including the caudate and putamen.¹ These areas of the brain appear to be associated with control of movement and may explain why motor symptoms, such as chorea, are prominent in patients with HD.

Many patients with HD exhibit progressive weight loss, suggestive of metabolic dysfunction.⁴ Wang and colleagues examined metabolic factors in patients with HD and found abnormal hormone levels (eg, ghrelin, glucagon, and amylin) that may contribute to food intake, absorption, and energy expenditure.⁴ They also found significantly decreased levels of cholesterol, an important substance for adult brain neuron function.⁴ This decrease may be linked to abnormal food digestion and absorption related to HD.^{4,6}

DISCLOSURES

Dr. Rosenblatt discloses he has served as a consultant and speaker for Lundbeck and as a consultant for Auspex Pharmaceuticals.

Dr. Frank discloses that he is principal investigator of the FIRST-HD/ARC-HD trials, which are funded by Auspex Pharmaceuticals.

BIOMARKERS

While there are no established biomarkers for disease onset or progression, biomarkers for HD are currently being investigated in numerous clinical trials of potential disease-modifying therapies. As a result of these investigations, biomarkers may, in the future, be helpful in clinical practice.

Brain-derived neurotrophic factor (BDNF) is a neurotrophic protein that aids in the growth and survival of neurons.⁷ BDNF deficiency has been linked to HD and it is thought that the increase of BDNF expression may be a viable strategy for disease treatment.⁷ Excessive quinolinic acid (QUIN) and kynurenine 3-monooxygenase (KMO) are under investigation as potential causal factors in HD pathology.⁸

Other biomarkers for HD may be detected on imaging studies, although, at present, these may be more useful as a research tool than as a clinical tool. Macrostructural brain imaging has shown a decline in striatal volume, cortical grey matter atrophy, and white matter volume reduction in patients with HD.¹ Decreased striatal volume, in particular, correlates to motor dysfunction and has been shown to occur more in patients with HD than age-matched controls.¹ Declines in striatal volume and white matter volume have been documented as occurring before motor symptoms present and a diagnosis of HD was made.

Brain abnormalities in HD have also been discovered using microstructural brain imaging. Measures of diffusion tensor imaging have uncovered abnormalities in patients with HD, including flaws in the neuronal fibre orientation and integrity of white matter and subcortical grey matter structures.¹

Imaging findings are useful in the research setting, particularly in clinical trials of potential HD treatments, but less so in the clinical setting. Typically, progression of disease will be fairly advanced before a patient has a demonstrable abnormal magnetic resonance image (MRI); it may be of little clinical value by that point. Nevertheless, the study of HD biomarkers has profound implications for the future of treatments. The discovery of new biomarkers for HD may ultimately aid researchers in the identification and development of new therapeutic treatment options.

The PREDICT-HD trial was designed to evaluate the natural history of the HD using a variety of tests (eg, imaging, motor, cognitive, functional, and psychiatric domains) and to identify new biomarkers that can be used

in the development of HD treatments.⁹ In 2014, investigators reported that 36 of the 39 measures studied showed longitudinal change over a 10-year period in individuals with premanifest HD. Imaging studies demonstrated a significant decrease in the putamen and caudate over the 10-year period, the highest effect size in the study. Motor dysfunction based on TMS scores was the second highest effect size. Patients also demonstrated significant declines in every measure of cognitive performance and there were changes noted in nearly all functional and psychiatric variables.

ENROLL-HD is a global, prospective, observational study in patients with HD that aims to collect a common set of data. The study also collects blood samples for DNA and cell lines. Both samples and data will be available for researchers to better understand the disease and to develop newer treatment options.¹⁰

NATURAL HISTORY

Differing criteria and categories have been proposed for the course of HD, but at the core of all classification systems is the divide between those patients who are not yet exhibiting symptoms (ie, premanifest) and those that are exhibiting symptoms (ie, manifest).¹

The premanifest period of HD is the time when a person with the *HTT* mutation does not show significant symptoms of disease to warrant a diagnosis. All patients diagnosed with HD are considered to be in the manifest period of the disease. Opinions vary on the subdivisions of the manifest period, but all agree that patients in the manifest period range from those who are active and functional to patients in need of caregiver or nursing facility support.

DIAGNOSIS

Signs and Symptoms

Huntington's disease is typically characterized by motor, cognitive, and behavioral symptoms.¹¹ Movement disorders are the most obvious symptoms and include both involuntary movement and impairment of voluntary movement. Involuntary movement, such as chorea, is the hallmark symptom of the disease and is more common in adult-onset HD.¹ The impairment of voluntary movement, however, is often much more debilitating and dominant in early-onset or juvenile HD.¹

Cognitive decline in HD is progressive and tends to include difficulty with attention, multitasking, problem solving, concentration, and judgment. Huntington's

disease appears to be associated with subcortical rather than cortical dementia.¹² Cognitive dysfunction always appears as HD progresses, but will vary among individuals. Cognitive impairments include deficiencies in working memory and visuomotor performance and subtle cognitive changes may appear up to 15 years earlier than motor symptoms.¹³ One estimate suggests that approximately 40% of patients with HD meet the criteria for mild cognitive impairment.¹³

Behavioral dysfunction is perhaps the most difficult symptom of HD to describe and predict. Depression is a common diagnosis in patients with HD and depressive symptoms are reported in over half of patients with HD.¹⁴ Even more common is a constellation of personality changes, which might be described as hypofrontal, where patients exhibit signs of apathy, irritability, disinhibition, obsessiveness, impulsiveness, and perseveration.¹² Apathy, in particular, is significantly increased among patients with HD compared with controls, but this may be because other neuropsychiatric symptoms (eg, depression) are more treatable with current pharmacological interventions and apathy is a known side effect of medications that reduce dopamine function.¹⁵ The incidence or rate of suicidal behavior is also increased among patients with HD.^{11,12} One study reported that 27% of patients with HD disclosed suicidal ideation and, of those, 10% revealed a history of suicide attempts.¹⁶ Another study noted suicide as the cause of death in >9% of patients with HD.¹⁷

Longitudinal studies, such as PREDICT-HD, have demonstrated that clinical symptoms of HD are evident long before an actual diagnosis is made. PREDICT-HD enrolled patients with a confirmed *HTT* mutation who are not yet diagnosed and reported that many patients were already showing subtle signs of impairment at the time of enrollment.¹⁸ While these findings may be suggestive of the need for earlier diagnosis, the potential impact on patients and families is unknown.¹⁸

The early presentation of HD evolves clinically over several years and a positive test for the *HTT* mutation is not itself grounds for a clinical diagnosis of HD. As standard practice, clinical diagnosis is made when the patient exhibits overt symptoms associated with the disease, typically motor symptoms (eg, chorea, dystonia), and has a family history of HD and/or a positive *HTT* mutation.

Patient History

The symptoms of HD often overlap with other neurodegenerative disorders; therefore it is important to obtain a comprehensive history of any patient suspected of having the disease. The physician should explore the family history and determine if any of the patient's relatives had HD. But just knowing a relative had HD is not enough—the physician should ask questions to more fully define the patient's risk. Was the relative definitely tested for HD (either by genetic testing or autopsy)? What was their age of onset? How long did this relative live with the disease? This background information will establish the patient's risk of having the HD mutation and probability that the presenting symptom represents the actual onset of the disease.

The physician may perform a mental status or basic cognitive examination with a standard measure, such as the Montreal Cognitive Assessment, to determine early signs of cognitive impairment. As part of the Unified Huntington's Disease Rating Scale, there are three other cognitive measures that can be used to monitor cognition over time.¹⁹ Further, the patient's psychiatric history should be explored, especially if there are reports of depression or personality changes. A focused quantitative neurologic examination may also be performed, looking for findings that are typical of HD.

Assessment Tools

Rating tools can be helpful to the physician when diagnosing HD. The Unified Huntington's Disease Rating Scale (UHDRS) developed by the Huntington Study Group is used almost universally in HD research today.¹⁹ While the UHDRS is primarily a research tool, it can have some utility in the clinical setting.

The Total Motor Score (TMS) is a well-established tool that is part of the UHDRS and generally takes about 10 to 15 minutes in the office setting. The TMS includes a standardized rating system of oculo-motor function, dysarthria, chorea, dystonia, gait, and postural stability (**Table 1**).¹⁹ The TMS is the total score of all individual motor ratings and a higher score is indicative of motor impairment. Most of the items are part of a standard neurological examination and may be tracked over time. The summed score can help with an overall impression of motor impairments or response to treatments. The items on this portion of the scale also highlight the fact that HD is more than just chorea.

In addition, physicians may want to consider focusing on ataxia and muscle stretch reflexes as additional relevant components of the neurological examination. It is important to remember that there is no absolute threshold or cutoff score to make a clinical diagnosis of HD and that many other neurologic conditions can elevate the TMS, so an elevated TMS does not establish that the patient definitely has HD.

The total functional capacity (TFC) score and the Independence scale portions of the UHDRS can also be used in clinical practice. The TFC is a 13-point scale that gauges the patient's abilities in 5 specific areas of functioning: occupation, finances, domestic chores, activities of daily living and place of residence. The total score can provide the physician with a picture of where the patient is at the time of the visit and over the course of time, and it is the primary research tool to monitor overall progression of disease. The Independence scale may be more appropriate for patients who have more advanced disease.

Quantitative motor (Q-motor) assessments are used in some ongoing treatment studies and have shown correlation to TMS scores.²⁰ Q-motor score consists of transducer-measured applied force techniques, including finger tapping, grip force, tongue protrusion, and choreatic movements.²¹ The ongoing TRACK-HD has documented a decline in Q-motor scores over a 36-month period.¹⁶

CURRENT TREATMENT OPTIONS

Pharmacologic

There is only one drug, tetrabenazine, approved by the US Food and Drug Administration (FDA) for the treatment of chorea associated with HD. It is associated with numerous side effects such as depressed mood, somnolence, akathisia, irritability, anxiety, insomnia, and parkinsonism. In addition, there is a black boxed warning for depression and suicidal thoughts and actions.^{22,23} When used, it is recommended that tetrabenazine be initiated at low doses and increased gradually until chorea is adequately treated or intolerable side effects emerge.

Guidelines are available for the treatment of chorea in HD, but have been met with some criticism given the limited studies available. The American Academy of Neurology, for example, recommends off-label use of riluzole and amantadine for the treatment of chorea, but this is not representative of current clinical practice.²⁴

TABLE 1. Components of the Total Motor Score of the UHDRS¹⁹

Ocular pursuit (horizontal and vertical)
Saccade initiation (horizontal and vertical)
Saccade velocity (horizontal and vertical)
Dysarthria
Tongue protrusion
Maximal dystonia (trunk and extremities)
Maximal chorea (face, mouth, trunk, and extremities)
Retropulsion pull test
Finger taps (left and right)
Pronate/supinate-hands (right and left)
Luria (fist-hand-palm test)
Rigidity-arms (right and left)
Bradykinesia-body
Gait
Tandem walking

Abbreviation: UHDRS, Unified Huntington's Disease Rating Scale.

Neuroleptic agents such as aripiprazole and olanzapine have been described in the literature as being tried in patients with HD, but neither is approved for use in this population and efficacy has not been established in controlled trials.²⁵

It is important to note that there are treatments available that may be appropriate for some patient symptoms but can have adverse effects that cause more harm than good in the patient with HD. For instance, anticholinergic bladder medications might be called for in certain patients with HD, but these drugs can negatively affect cognition.

Nonpharmacologic

Since pharmacologic therapy is so limited for the patient with HD, it is important to offer suggestions that may provide psychosocial support. Building a daily routine, for example, can be very beneficial for patients. The physician can also recommend that the patient make lists and break down tasks into individual steps because patients with HD may be easily overwhelmed when multitasking.

In addition, allied health professionals are key to the overall management of HD related symptoms. Commonly, over the course of their illness, patients may

need the services from social work, physical therapy, occupational therapy, speech pathologists, genetic counseling, and other professionals.

THERAPEUTICS UNDER INVESTIGATION

As we look toward future treatment options for HD, it is important to note the challenges associated with developing treatments for this type of disease. Since there is no biological marker to monitor change in disease, disease-modifying trials in HD will typically require a lengthy clinical trial with a large patient cohort to effectively study a drug.

Despite the challenge associated with outcome measures and treatment development, there are several ongoing trials designed to offer new therapy options for patients with HD and physicians treating the disease. The ultimate goal, of course, is to make HD a more treatable condition. What follows is a brief review of some of the more prominent ongoing studies in HD treatment research (Table 2).

REACH2HD

PBT2 is a metal protein-attenuating compound that is thought to reduce the metal-induced aggregation of the mutant huntingtin protein. Brain MRI has shown that patients with HD have increased concentrations of iron in the basal ganglia and the cortex that is associated with CAG repeat number. PBT2 was previously studied in Alzheimer's disease and did show some promising results in neuropsychological testing.²⁶ As a result, researchers aimed to evaluate PBT2 in patients with HD.

Investigators recently published safety results of the trial and reported that the PBT2 was generally safe and well tolerated in patients with HD.²⁶ Researchers cited some improvement on cognitive scales in this early publication, but the results need to be replicated in a large-scale trial.

HART and PRIDE-HD

Pridopidine is a dopaminergic stabilizer that can increase or decrease psychomotor activity contingent upon the initial degree of activity. HART was a 12-week randomized, double-blind, placebo-controlled trial of 227 subjects in the United States and Canada that investigated pridopidine in patients with HD. The primary outcome of the study was change in the modified motor score, part of the TMS.²⁷ The results of the trial, while not significant, did show

improvement in motor function for patients with HD compared with placebo.

The PRIDE-HD study is an ongoing 26-week, phase II, randomized, double-blind, placebo-controlled study of pridopidine for the treatment of motor impairments in patients with HD. Patients in the trial must have diagnosed HD, including clinical symptoms and a positive *HTT* mutation test. The primary endpoint of the study is change in TMS score. Secondary endpoints include scores of the physical performance test and safety and tolerability across a range of doses. Results of the study are expected in 2015.²⁸

FIRST-HD and ARC-HD

Deuterated tetrabenazine (SD-809) is in development for the treatment of chorea associated with HD. SD-809 has the same mechanism of action as tetrabenazine, but through the use of deuterium technology, chemical modifications were made to the tetrabenazine molecule to create a new form of the drug. This reduces the breakdown of the active metabolites in the drug, giving SD-809 a different pharmacokinetic profile compared with tetrabenazine.²⁹

SD-809 is currently involved in 2 separate phase III trials. FIRST-HD is a randomized, double-blind study of patients who have not taken tetrabenazine with the goal of evaluating the safety, tolerability, and efficacy of SD-809 for treating HD-related chorea. ARC-HD is an open-label, long-term trial that includes patients who are currently taking tetrabenazine to evaluate safety and provide guidance on how to switch patients from tetrabenazine to SD-809.²⁹

CYST-HD

Delayed-release cysteamine bitartrate (RP103) is a cystine-depleting agent approved for use in the treatment of nephropathic cystinosis and currently under investigation in HD. Cysteamine may induce responses in the brain that reduce cellular oxidative stress. Through inhibition of several intracellular enzymes, such as transglutaminase, cysteamine inhibits protein aggregation, which is known to form in HD. Cysteamine is also responsible for increasing BDNF, which is deficient in both HD and Alzheimer's disease patients.³⁰

An 18-month analysis of RP103 in a double-blind, placebo-controlled phase II/III trial in patients with HD (n=96) was presented at the 2014 meeting of the Huntington Study Group. The primary endpoint was change in the TMS score of UHDRS from baseline to

TABLE 2. Clinical Trials of Huntington's Disease Treatments

Study Drug	Study Name	Sponsor	Study Design	Phase	Clinicaltrials.gov Identifier	Primary Endpoint	Status
PBT2 ²⁶	REACH-2HD	Prana Biotechnology Limited	26-Week, randomized, double-blind, placebo-controlled study	II	NCT01590888	Safety and tolerability	Completed; PBT2 generally safe and well tolerated
Pridopidine ²⁷	HART	Teva Pharmaceutical Industries	12-Week, randomized, double-blind, placebo-controlled study	II	NCT00724048	MMS	Study completed; results showed improvement in MMS score ($P = NS$)
Pridopidine ²⁸	PRIDE-HD	Teva Pharmaceutical Industries	26-Week, randomized, parallel-group, double-blind, placebo-controlled study	II	NCT02006472	TMS	Ongoing; estimated completion date is March 2015
SD-809 (dutetrabenazine) ²⁹	FIRST-HD	Auspex Pharmaceuticals, Inc.	12-Week, randomized, double-blind, placebo-controlled study	III	NCT01795859	TMC	Study completed; results expected early 2015
SD-809 (dutetrabenazine) ²⁹	ARC-HD	Auspex Pharmaceuticals, Inc.	Long-term, open-label, safety study	III	NCT01897896	Incidence of AEs	Ongoing
RP103 (delayed-release cysteamine) ³⁰	CYST-HD	Raptor Pharmaceuticals Inc.	3-Year, double-blind, placebo-controlled study	II/III	–	TMS	Ongoing
Laquinimod ³¹	LEGATO-HD	Teva Pharmaceutical Industries	12-Month, multicenter, multinational, randomized, double-blind, placebo-controlled, parallel-group study	II	NCT02215616	TMS	Ongoing; estimated completion date is January 2017
PF-0254920 ³²	PF-0254920	Pfizer	28-Day, double-blind, randomized, sequential treatment group, placebo-controlled study	II	NCT01806896	TMS	Ongoing; estimated completion date is November 2015
Coenzyme Q10	2CARE	National Institute of Neurological Disorders and Stroke (NINDS)	Long-term, randomized, placebo-controlled study	III	NCT00608881	TFC	Study discontinued due to fertility
Creatine	CREST-E	National Center for Complementary and Alternative Medicine (NCCAM)	Long-term, randomized, double-blind placebo-controlled study	III	NCT00712426	TFC	Study discontinued due to fertility

Abbreviations: AE, adverse event; MMS, modified motor score; TFC, total functional capacity; TMC, total maximal chorea; TMS, total motor score.

18 months between RP103 and placebo. The results indicated a change of 4.5 points vs 6.7, respectively ($P = 0.19$). This study is ongoing.

LEGATO-HD

Laquinimod is a small molecule that is thought to decrease inflammatory activity in the brain. Laquinimod is being developed as a central nervous system-active immunomodulator for the treatment of several neurological diseases, including relapsing-remitting multiple sclerosis, progressive multiple sclerosis, and HD.

LEGATO-HD is a phase II, multicenter, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the safety and efficacy of laquinimod in patients with HD. The primary endpoint of this study is the TMS. The trial has recently begun screening patients and results are expected in late 2015.³¹

PF-0254920

PF-0254920 is an inhibitor of phosphodiesterase 10A, an enzyme found primarily in the striatum. It is being studied in a 26-week, phase II, randomized, parallel-group, double-blind comparison of 2 doses (5 mg and 20 mg) and placebo. The primary endpoint of the study is treatment of motor dysfunction in patients with HD using TMS. The trial is ongoing and results are not expected until early 2016.³²

REAP-HD

Reducing Anti-Psychotic use in residential care—Huntington's Disease (REAP-HD) is examining the decrease in antipsychotic use in patients with HD using the REAP-HD program compared with standard staff education. The goal of the study is to reduce antipsychotic prescribing in this population because of the modest benefits and potential harms associated with this drug class in patients with HD.³³ REAP-HD is based in New South Wales, Australia.

Discontinued Trials

2CARE

The 2CARE was a randomized, double-blind study investigating coenzyme Q10, as treatment for the functional decline in HD. Coenzyme Q10 is a naturally occurring substance in the body that aids in the process of energy creation. The study was stopped in July 2014 due to futility.

CREST-E

Creatine was studied in the CREST-E trial as a treatment to slow the progressive functional decline inherent in HD. CREST-E was a multi-center, randomized, double-blind, placebo-controlled clinical trial and was halted in October 2014 due to futility.

CONCLUSION

Huntington's disease is an inherited, progressive condition that is irrevocably fatal. Patients typically live approximately 10 to 20 years after the onset of motor symptoms and patient burden progresses with the disease, ultimately requiring complete assistance in activities of daily living. At present, there is a dearth of treatment options available for patients with the disease and the medications that are available address the symptoms of HD without altering the underlying disease process.

We believe there are reasons to be optimistic. Ongoing observational trials continue to document the natural history of HD and discover new biomarkers to guide treatment development. Potential disease-modifying therapies are currently under investigation showing some promise as future treatment options. Researchers are also developing symptom-focused therapies that may improve upon the medications already available, but with fewer adverse effects. We hope that the research described here will offer treatment options that enable patients to live more meaningful lives.

REFERENCES

1. Ross CA, Aylward EH, Wild EJ, et al. Huntington disease: natural history, biomarkers and prospects for therapeutics. *Nat Rev Neurol*. 2014;10(4):204-216.
2. Roos RAC. Huntington's disease: a clinical review. *Orphanet J Rare Dis*. 2010;5:40.
3. Gusella JF, MacDonald ME, Lee JM. Genetic modifiers of Huntington's disease. *Mov Disord*. 2014;29(11):1359-1365.
4. Wang R, Ross CA, Cai H, et al. Metabolic and hormonal signatures in pre-manifest and manifest Huntington's disease patients. *Front Physiol*. 2014;5:231.
5. Myers RH. Huntington's disease genetics. *NeuroRx*. 2004;1(2):255-262.
6. Valenza M, Rigamonti D, Goffredo D, et al. Dysfunction of the cholesterol biosynthetic pathway in Huntington's disease. *J Neurosci*. 2005;25(43):9932-9939.
7. Baydyuk M, Xu B. BDNF signaling and survival of striatal neurons. *Front Cell Neurosci*. 2014;8:254.
8. Schwarcz R, Guidetti P, Sathyaikumar MV, Muchowski PJ. Of mice, rats, and men: revisiting the quinolinic acid hypothesis of Huntington's disease. *Prog Neurobiol*. 2010;90(2):230-245.

9. Paulsen JS, Long JD, Johnson HJ, et al; PREDICT-HD Investigators and Coordinators of the Huntington Study Group. Clinical and biomarker changes in premanifest Huntington disease show trial feasibility: a decade of the PREDICT-HD study. *Front Aging Neurosci.* 2014;6:78.
10. Seay M, Giuliano J, Handley O; Enroll HD Steering Committee. Enroll-HD: a prospective observational study in a global Huntington's disease cohort. *J Neurol Neurosurg Psychiatry.* 2012;83(suppl 1):A46-A47.
11. Dorsey ER, Beck CA, Darwin K, et al; Huntington Study Group COHORT Investigators. Natural history of Huntington disease. *JAMA Neurol.* 2013;70(12):1520-1530.
12. Ha AD, Fung VS. Huntington's disease. *Curr Opin Neurol.* 2012;25(4):491-498.
13. Duff K, Paulsen J, Mills J, et al. Mild cognitive impairment in prediagnosed Huntington disease. *Neurology.* 2010;75(6):500-507.
14. Thompson JC, Harris J, Sollom AC, et al. Longitudinal evaluation of neuropsychiatric symptoms in Huntington's disease. *J Neuropsychiatry Clin Neurosci.* 2012;24(1):53-60.
15. Tabrizi SJ, Scahill RI, Owen G, et al; TRACK-HD Investigators. Predictors of phenotypic progression and disease onset in premanifest and early-stage Huntington's disease in the TRACK-HD study: analysis of 36-month observational data. *Lancet Neurol.* 2013;12(7):637-649.
16. Wetzel HH, Gehl CR, Dellefave-Castillo L, Schiffman JF, Shannon KM, Paulsen JS; Huntington Study Group. Suicidal ideation in Huntington disease: the role of comorbidity. *Psychiatry Res.* 2011;188(3):372-376.
17. Di Maio L, Squitieri F, Napolitano G, Trofatter JA, Conneally PM. Suicide risk in Huntington's disease. *J Med Genet.* 1993;30(4):293-295.
18. Biglan KM, Zhang Y, Long JD, et al; PREDICT-HD Investigators of the Huntington Study Group. Refining the diagnosis of Huntington disease: the PREDICT-HD study. *Front Aging Neurosci.* 2013;5:12.
19. Huntington Study Group. Unified Huntington's disease rating scale: reliability and consistency. *Mov Disord.* 1996;11(2):136-142.
20. Sampaio C, Borowsky B, Reilmann R. Clinical trials in Huntington's disease: interventions in early clinical development and newer methodological approaches. *Mov Disord.* 2014;22(11):1419-1428.
21. Tabrizi SJ, Scahill RI, Durr A, et al; TRACK-HD Investigators. Biological and clinical changes in premanifest and early stage Huntington's disease in the TRACK-HD study: the 12-month longitudinal analysis. *Lancet Neurol.* 2011;10(1):31-42.
22. Huntington Study Group. Tetrabenazine as antichorea therapy in Huntington disease: a randomized controlled trial. *Neurology.* 2006;66(3):366-372.
23. Xenazine [package insert]. Deerfield, IL; Lundbeck; 2012.
24. Reilmann R. Pharmacological treatment of chorea in Huntington's disease—good clinical practice versus evidence-based guideline. *Mov Disord.* 2013;28(8):1030-1033.
25. Frank S. Treatment of Huntington's disease. *Neurotherapeutics.* 2014;11(1):153-160.
26. Huntington Study Group Reach2HD Investigators. Safety, tolerability, and efficacy of PBT2 in Huntington's disease: a phase 2 randomised, double-blind, placebo-controlled trial. *Lancet Neurol.* 2015;14(1):39-47.
27. Huntington Study Group HART Investigators. A randomized, double-blind, placebo-controlled trial of pridopidine in Huntington's disease. *Mov Disord.* 2013;38(10):1407-1415.
28. Teva Branded Pharmaceutical Products R&D, Inc. A Phase 2, Dose-Finding, Randomized, Parallel-Group, Double-Blind, Placebo-Controlled Study, Evaluating the Safety and Efficacy of Pridopidine 45 mg, 67.5 mg, 90 mg, and 112.5 mg Twice-Daily Versus Placebo for Symptomatic Treatment in Patients With Huntington's Disease. In: clinicaltrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000-2014. Available from: <http://www.clinicaltrials.gov/ct2/show/NCT02006472>. NLM identifier: NCT02006472.
29. Testa C, Stamler D, Frank S. Testing the safety and efficacy of SD-809 for symptomatic treatment of chorea in Huntington disease. *Neurotherapeutics.* 2014;11(1):222. Poster 16.
30. Bonneau D, Bachoud Lévi AC, Durr A, et al. Cysteamine potentially slows motor deterioration in early stage Huntington's disease: an 18-month randomized, double-blind, placebo-controlled, multicenter trial. Presented at: Huntington Study Group 2014: Ideas for the Future; November 6-8, 2014; Minneapolis, MN.
31. Teva Branded Pharmaceutical Products R&D, Inc. A Multicenter, Multinational, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Laquinimod (0.5, 1.0 and 1.5 mg/Day) as Treatment in Patients With Huntington's Disease. In: clinicaltrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000-2014. Available from: <http://www.clinicaltrials.gov/ct2/show/NCT02215616>. NLM identifier: NCT02215616.
32. Pfizer. A Phase 2, Double-blind Randomized, Sequential Treatment Group, Placebo-controlled Study To Evaluate The Safety, Tolerability And Brain Cortico-striatal Function Of 2 Doses Of Pf-02545920 In Subjects With Early Huntington's Disease In: clinicaltrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000-2014. Available from: <http://www.clinicaltrials.gov/ct2/show/NCT01806896>. NLM identifier: NCT01806896.
33. Loy CT, Hayen A, McKinnon C. Protocol for Reducing Anti-Psychotic use in residential care-Huntington disease (REAP-HD): a pilot cluster randomized controlled trial of a multifaceted intervention for health professionals. *BMJ Open.* 2014;4:e006151.

