Huntington's disease



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Aspen course
2026

Disclosures

- Grants/research support: Lewy Body Dementia Association, Michael J. Fox Foundation
- Honoraria: International Parkinson Disease and Movement Disorders Society, Lewy Body Dementia Association, Michael J. Fox Foundation, Parkinson's Foundation
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- Board/leadership positions: Chair of the Lewy Body Dementia Association (LBDA) Industry Advisory Council; LBDA Board of Directors, Member at large; International Consortium for Dementia with Lewy Bodies, Executive Committee member; KeifeRx Scientific Advisory Board; Secretary of the International Parkinson and Movement Disorder Society

- Off-label medication use

HD overview

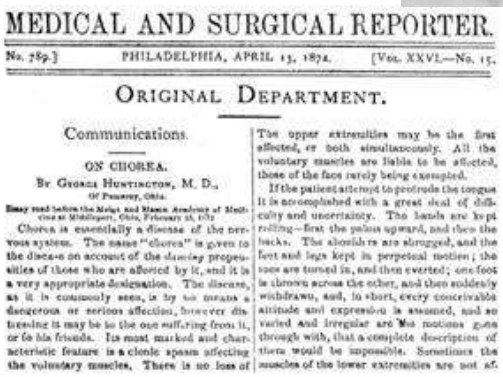
- Autosomal dominant inheritance
- Gene mutation, huntingtin (htt) gene, short arm 4th chromosome (Chr 4p16.3)
- Expanded CAG repeats
- Exon 1 of htt gene
- Adult onset, rare juvenile
- Mean duration 17-20 years
- Clinical triad

George Huntington (1850-1916)



- On Chorea (1872)

- Described cardinal features
  - Adult onset
  - Hereditary
  - Abnormal movements
  - Behavioral issues
  - Progressive



MEDICAL AND SURGICAL REPORTER.

No. 789.] PHILADELPHIA, APRIL 13, 1872. [Vol. XXVI.—No. 15.

ORIGINAL DEPARTMENT.

Communications.

ON CHOREA.

By George Huntington, M. D.,

Of Pomeroy, Ohio.

Essay read before the Meigs and Mason Academy of Medicine at Middleport, Ohio, February 13, 1872.

Chorea is essentially a disease of the nervous system. The name "chorea" is given to the disease on account of the dancing propensities of those who are affected by it, and it is a very appropriate designation. The disease, as it is commonly seen, is by no means a dangerous or serious affection, however distressing it may be to the one suffering from it, or to his friends. Its most marked and characteristic feature is a clonic spasm affecting the voluntary muscles. There is no loss of

The upper extremities may be the first affected, or both simultaneously. All the voluntary muscles are liable to be affected, those of the face rarely being exempted.

If the patient attempt to protrude the tongue it is accomplished with a great deal of difficulty and uncertainty. The hands are kept rolling—first the palms upward, and then the backs. The shoulders are shrugged, and the feet and legs kept in perpetual motion; the toes are turned in, and then everted; one foot is thrown across the other, and then suddenly withdrawn, and, in short, every conceivable attitude and expression is assumed, and so varied and irregular are the motions gone through with, that a complete description of them would be impossible. Sometimes the muscles of the lower extremities are not af-



DORSAL COLUMN

Grey Matter

George Huntington: a legacy of inquiry, empathy and hope

Alice Wexler,[1] Edward J. Wild[2] and Sarah J. Tabrizi[2]

*On 12 June 1806, in the long-established farming and fishing village of East Hampton, at the far eastern end of Long Island, about 60 miles northeast of New York City, USA, Captain David Hedges, a member of the local gentry, awoke to find his wife missing. A search 'thro fields of grain to the shore' did not find her 'and there is every reason to believe she has **precipitated herself into the surf',** reported the local newspaper. 'Mrs. Hedges was about **40 years of age**, and was much esteemed by her neighbors' the obituary continued. 'This extraordinary step is attributed to her **extreme dread of the disorder called St. Vitus' dance**, with which she **began to be affected**, and which her **mother now has to a great degree**. From some arrangements of her clothing it appears she had for some time contemplated her **melancholy** end.' (The Suffolk Gazette, 30 June 1806).*



Genetic History of HD - Seminal events

- 1972 - Centennial celebration of Huntington's paper
- Venezuela project – description of HD families around Lake Maracaibo in Venezuela
- 1979 – First American expedition to Maracaibo
- 1983 - Discovery of location of genetic marker (Gusella et al., 1983)
- 1993 – Identification of abnormal HD gene – CAG repeat (HD Collaborative Research Group 1993)

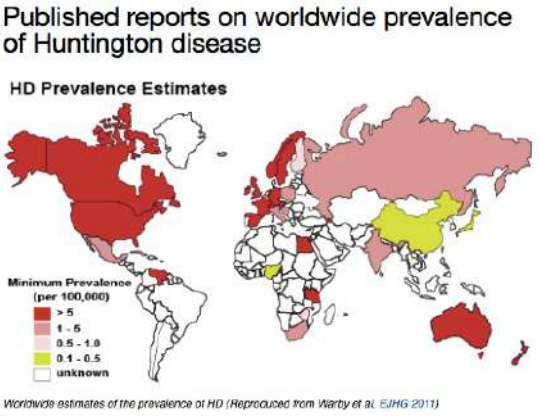




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Epidemiology

- Prevalence estimates vary across the world
- ~7-10 cases per 100,000 in White populations
  - Less in Black and Asian populations
- 2.3-17.4/100,000 in USA (~1/7300)
- 560/100,000 (Moray Firth, Scotland)
- 700/100,000 (Lake Maracaibo, Venezuela)



- Incidence ~1/10,000; ~30,000 in US

- Founder effects in some populations
- Increased prevalence over past 2 decades with increased availability of genetic testing

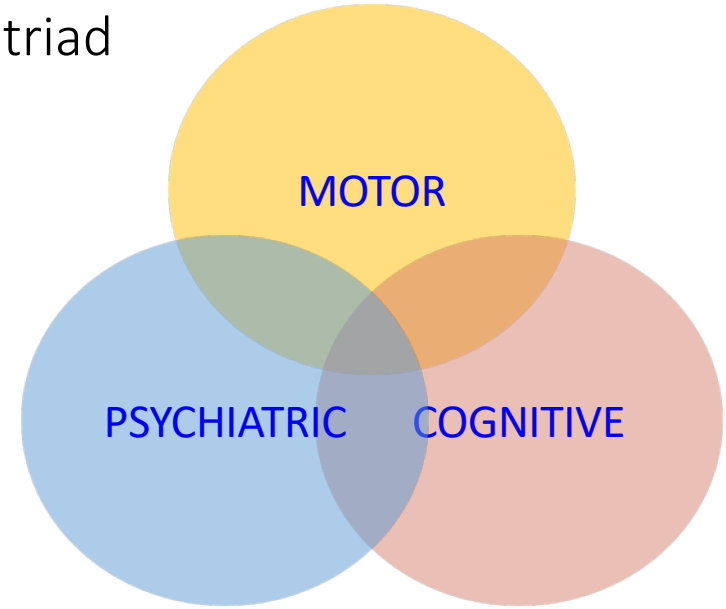
http://www.cmmt.ubc.ca Harper and Jones 2002; Walker 2007; Rawlins 2016

Video





HD – Classic clinical triad



Motor

Chorea
Oculomotor abnormalities (impaired saccades)
Dystonia (cranial, cervical, truncal, limb, bruxism)
Tics or “tourettism”
Myoclonus
Bradykinesia
Rigidity
Gait difficulty, postural instability, ataxia
Motor impersistence, with dropping things, dipping gait
Dysarthria
Dysphagia
Juvenile phenotype - dystonia, parkinsonism, myoclonus

Psychiatric

- Dysphoria, agitation, irritability, apathy, anxiety – 65%
- Depression 33-70%
- Apathy ~50%
- OCD/OCB 10-50%
- Delusions, compulsions 5-12%
- Hypersexuality, hallucinations <5%

Depression

- Frequency in lifetime in adults affected by or at-risk for HD – 38% and of gene+ only, 43% (Clark et al., 2023)
- Suicide (5-10% > general population)

Apathy

- More common in manifest HD (24-76%) vs. pre-manifest HD (10-33%) (Zadegan et al., 2023)
- Greater in later stage HD (Gunn et al., 2023)
- May be associated with cognitive decline and distinct from depression (Connors et al., 2023)

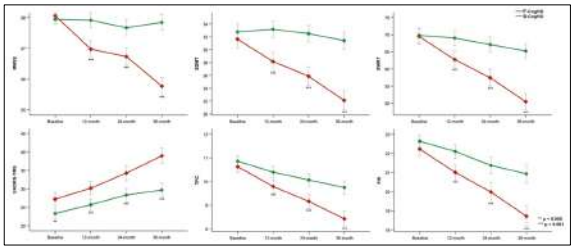
OCD/OCB

- Greater in later stage HD
- May be distinct but related to perseverative behaviors (Zadegan et al., 2024)

Paulsen et al., 2001; Walker 2007; Clark et al., 2023; Gunn et al., 2023; Zadegan et al., 2023, 2024; Connors et al., 2023; Zadegan et al., 2025

Cognitive

"Subcortical dementia"
Executive function
Processing speed
Memory
Verbal fluency
Visuoperceptual and construction
Judgment
Insight
Social cognition
Functional impairment
MCI in ~40% of prodromal HD on standardized tests



- Distinct cognitive progression phenotypes over 3 years (fast vs. slow) (Martinez-Horta et al., 2023)
  - Enroll-HD
  - Faster group – higher motor scores, greater decline in function and TFC

Peavy et al., 2010; Duff et al., 2010; Paulsen et al., 2011; Mestre et al., 2017; Eddy et al., 2022; Horta-Barba et al., 2023; Martínez-Horta et al., 2023; Jellinger 2024

Systemic Symptoms in Huntington's Disease: A Comprehensive Review

Raja Mehanna, MD[1]* and Joseph Jankovic, MD[2]

- Systematic review of systemic and autonomic symptoms → 123 articles
- Cardiovascular
  - Nocturnal non-dipping of BP
- Respiratory
- Gastrointestinal
  - Dysphagia
  - Weight loss
- Urinary
  - Incontinence, frequency, urgency
- Sexual
- Thermoregulatory

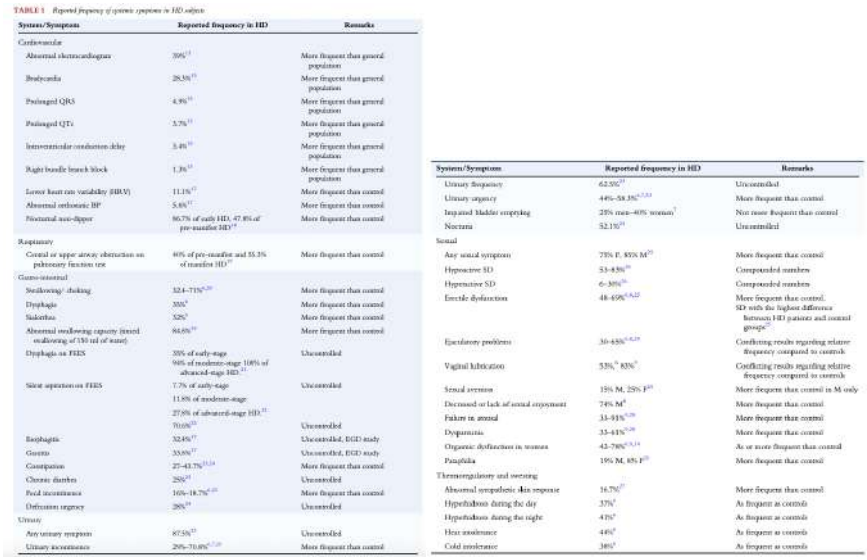


TABLE 1 Reported frequency of systemic symptoms in HD subjects

System/Symptom	Reported frequency in HD	Remarks
Cardiovascular		
Abnormal electrocardiogram	39%[13]	More frequent than general population
Bradycardia	28.5%[13]	More frequent than general population
Prolonged QRS	4.9%[13]	More frequent than general population
Prolonged QTc	5.7%[13]	More frequent than general population
Intraventricular conduction delay	3.4%[13]	More frequent than general population
Right bundle branch block	1.3%[13]	More frequent than general population
Lower heart rate variability (HRV)	11.1%[17]	More frequent than control
Abnormal orthostatic BP	5.6%[17]	More frequent than control
Nocturnal non-dipper	86.7% of early HD, 47.8% of pre-manifest HD[3,4]	More frequent than control
Respiratory		
Central or upper airway obstruction on pulmonary function test	46% of pre-manifest and 55.2% of manifest HD[17]	More frequent than control
Gastro-intestinal		
Swallowing/ choking	324–715%[6,20]	More frequent than control
Dysphagia	300%[5]	More frequent than control
Sialorrhea	52%[5]	More frequent than control
Abnormal swallowing capacity (timed swallowing of 150 ml of water)	84.6%[10]	More frequent than control
Dysphagia on FEES	35% of early-stage 90% of moderate-stage 100% of advanced-stage HD[21]	Uncontrolled
Silent aspiration on FEES	7.7% of early-stage 11.8% of moderate-stage 27.8% of advanced-stage HD[21]	Uncontrolled
	70.6%[22]	Uncontrolled
Esophagitis	32.4%[17]	Uncontrolled, EGD study
Gastritis	33.8%[17]	Uncontrolled, EGD study
Constipation	27–42.7%[13,14]	More frequent than control
Chronic diarrhea	25%[14]	Uncontrolled
Fecal incontinence	16%–18.2%[6,20]	More frequent than control
Defecation urgency	28%[14]	Uncontrolled
Urinary		
Any urinary symptom	87.5%[23]	Uncontrolled
Urinary incontinence	29%–70.8%[6,7,20]	More frequent than control

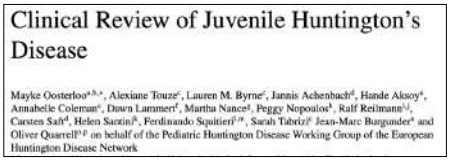
System/Symptom	Reported frequency in HD	Remarks
Urinary frequency	62.5%[23]	Uncontrolled
Urinary urgency	44%–58.3%[6,7,23]	More frequent than control
Impaired bladder emptying	25% men–40% women[7]	Not more frequent than control
Nocturia	52.1%[24]	Uncontrolled
Sexual		
Any sexual symptom	75% F, 85% M[25]	More frequent than control
Hyperactive SD	53–85%[26]	Compounded numbers
Hyporactive SD	6–30%[26]	Compounded numbers
Erectile dysfunction	48–69%[6,8,22]	More frequent than control; SD with the highest difference between HD patients and control groups[22]
Ejaculatory problems	30–65%[6,8,29]	Conflicting results regarding relative frequency compared to controls
Vaginal lubrication	53%,[6] 83%[8]	Conflicting results regarding relative frequency compared to controls
Sexual aversion	19% M, 25% F[25]	More frequent than control in M only
Decreased or lack of sexual enjoyment	74% M[8]	More frequent than control
Failure in arousal	33–91%[6,29]	More frequent than control
Dyspareunia	33–41%[6,29]	More frequent than control
Orgasmic dysfunction in women	42–78%[6,8,14]	As or more frequent than control
Paraphilia	19% M, 8% F[30]	More frequent than control
Thermoregulatory and sweating		
Abnormal sympathetic skin response	16.7%[17]	More frequent than control
Hyperhidrosis during the day	37%[5]	As frequent as controls
Hyperhidrosis during the night	43%[5]	As frequent as controls
Heat intolerance	44%[6]	As frequent as controls
Cold intolerance	36%[6]	As frequent as controls

Mehanna & Jankovic 2024

Juvenile HD ("Westphal variant")

- Age of onset ≤ 20
- 5-15% of HD cases
- AD but typically paternal transmission
- CAG repeats > 50

- Initial features – motor symptoms (parkinsonism, bradykinesia, rigidity, dystonia – and less chorea), behavioral, cognitive
- Other – leg stiffness, scissoring gait, toe walking, clumsiness, decline of mental function and milestones, decline in school performance, behavioral changes, pain, itching
- Later features – dementia, dysarthria, abnormal eye movements, tremor, ataxia, myoclonus, seizures
- Duration of illness 5-15 years
- Potential biomarkers – MRI with atrophy in striatum and thalamus, NfL



Clinical Review of Juvenile Huntington's Disease

Mayke Oosterloo[a,b,*], Alexiane Touze[c], Lauren M. Byrne[c], Jannis Achenbach[d], Hande Aksoy[e], Annabelle Coleman[c], Dawn Lammert[f], Martha Nance[g], Peggy Nopoulos[h], Ralf Reilmann[i,j], Carsten Saft[d], Helen Santini[k], Ferdinando Squitieri[l,m], Sarah Tabrizi[c], Jean-Marc Burgunder[n] and Oliver Quarrell[o,p] on behalf of the Pediatric Huntington Disease Working Group of the European Huntington Disease Network



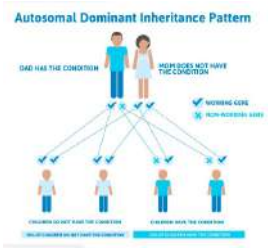
Pediatric Huntington Disease Brains Have Distinct Morphologic and Metabolic Traits: the RAREST-JHD Study

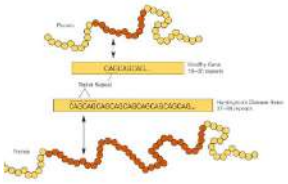
Maria Eugenia Caligiuri, PhD,[1] Emanuele Tinelli, MD, PhD,[1,2] Patrizia Vizza, PhD,[1] Giusy Giancotterino, PSc,[1] Francesco Cicone, MD, PhD,[1] Giuseppe Lucio Cascini, MD,[1,2] Umberto Sabatini, MD,[1,2] and Ferdinando Squitieri, MD, PhD[3,4]

Greater striatal atrophy in POHD (n= 5) vs. AOHD (n= 14). Widespread, significantly altered glucose metabolism occurred in several different POHD cortical areas and thalamus, but not AOHD cortex, consistent with differences in clinical progression.

Byrne et al., 2022; Schultz et al., 2023; Oosteroo et al, 2024; Caligiuri et al., 2024

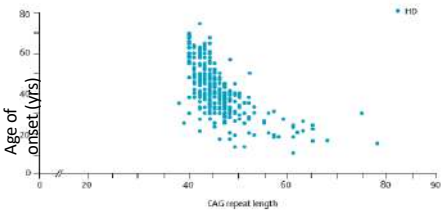
HD – Genetics and CAG repeats





CAG Repeat length	Interpretation	Risk
<27	Normal	•No disease •No known risk to children
27-35	Intermediate (normal, mutable)	•No symptoms •Small risk to children with expansion
36-39	Reduced penetrance (abnormal)	•May or may not have symptoms •50% risk to children
>39	**Full penetrance (abnormal)**	•Symptoms

HD – Age of onset and CAG repeat length



Walker 2007

Intermediate alleles (27-35 repeats)

- Case reports
  - Autopsy proven HD with 29 CAG repeats
  - Late onset – 82 year old with 2 year h/o chorea (CAG 29)

- Prospective Huntington At Risk Observational Study (PHAROS)
  - 50/983 (5.1%) had intermediate alleles (IA) 27-35 repeats
  - IA were similar to controls (<26 CAG) on UHDRS motor, cognitive, and functional measures
  - IA were worse on behavioral scores, apathy and suicidal ideation than controls

- European registry study
  - 657/12,190 (5.38%) had < 36 CAG with 76 IA carriers (11.56%), 581 controls (88.44%)
  - No sig differences in outcome measures but an effect of age
  - Older IAs had higher chorea vs. controls (p=0.001) and at 1-year, IA carriers had greater cognitive decline (p=0.002)

Kenney et al., 2007; Squitieri et al., 2012; Killoran et al., 2013; Garcia-Ruiz et al., 2016; Cubo et al., 2016; Heinzmann et al., 2023

CAG repeat transmission

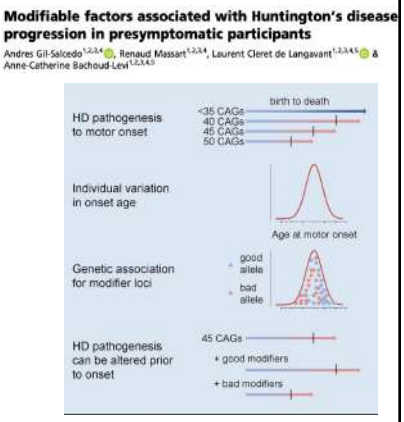
- CAG repeats > 28 show instability on replication
- Most instability leads to expansion (73%)
- Contraction can also occur (23%)
- Greater instability with spermatogenesis
- Greater anticipation with paternal transmission

“Sporadic” HD

- No known family history may be as high as 8% of all individuals with HD
- Rare, de novo expansion from nonpenetrant but unstable repeats (27-35 range)
- Other factors:
  - Anticipation (child before parent)
  - Early death or misdiagnosis
  - Adoption
  - False paternity

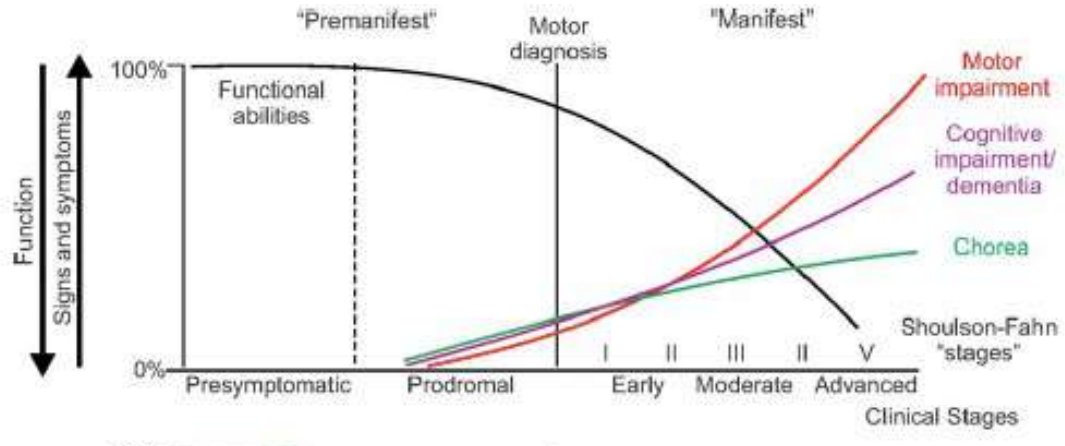
Modifiers for age of onset

- GWAS reveal loci that modify the age at onset of HD
  - Effects at chr15 locus (FAN1) hasten or (MTMR10) delay onset by 6 or 1.4 years, respectively
  - A single effect at chr8 locus hastens onset by 1.6 years (RRM2B, UBR5)
  - MLH1 association & pathway analysis implicate DNA handling in disease modification
- Substance abuse (tobacco, etoh, drugs) associated with earlier age of motor onset (AMO), Enroll-HD
  - Women abstaining from drugs delayed AMO by 4.6 years
  - Abstinence from tobacco delayed AMO by 2.3 years
- Other factors - High level of education, BMI <23 kg/m2 before age 40 and >23 kg/m2 thereafter, etoh consumption <15units/week, current coffee consumption and no smoking linked to slow disease progression. Also no previous exposure to antidepressants or anxiolytic, no psychiatric history/comorbidities, and female.



Tome et al., 2013; Gusella et al., 2015; Hensman Moss et al., 2017; Flower et al., 2019; Schultz et al., 2017; Gil-Salcedo et al., 2024

HD progression



Reilmann et al., 2014

Influences on onset and/or progression

Biological	• Plasma and CSF metabolome, over 3 years, differences in faster progressors (e.g., greater oxidative stress and inflammation, disturbances in NO and urea metabolism, lower polyamines, elevated glucose, deficient AMPK signaling)
Sex/ sex hormones	• ? Effects on symptoms, onset
Race/ ethnicity	• Enroll-HD database, baseline & follow up (≤ 2000 days) • Lower TFC, motor and cognitive scores in Black compared to White, Asian, and Hispanic patients. • No significant differences over time.

An exploratory metabolomic comparison of participants with fast or absent functional progression from 2CARE, a randomized, double-blind clinical trial in Huntington's disease

Racial Differences in the Presentation and Progression of Huntington's Disease

Disparities in Huntington Disease Severity: Analysis Using the ENROLL-HD Dataset

Association between sex and Huntington's disease: an updated review on symptomatology and prognosis of neurodegenerative disorders

Unraveling progression subtypes in people with Huntington's disease

Buchanan et al., 2023; Mendizabal et al., 2023; Hasnain et al., 2024; Raschka et al., 2024; McGarry et al., 2024

Lifecycle

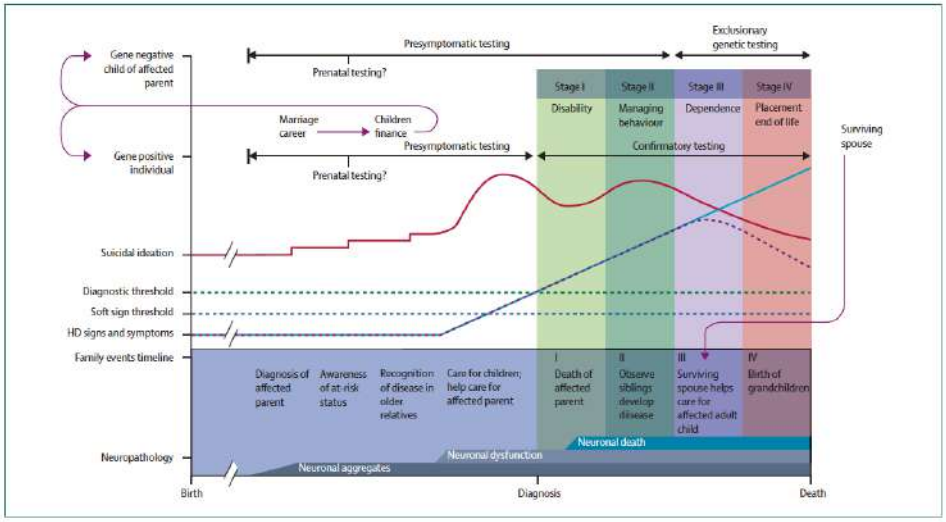


Figure 4: Life cycle in Huntington's disease
This figure depicts the sequential evolution of events and ultimately recurrent nature of Huntington's disease from the perspective of a child born to an affected parent. The family events timeline shows events that might occur in different sequences for different individuals; irrespective of timing, such events can have clinically significant implications.

Walker 2007

A biological classification of Huntington's disease: the Integrated Staging System

Sarah J Tabrizi, Scott Schobel*, Emily C Gantman, Alexandra Mansbach, Beth Borowsky, Pavlina Konstantinova, Tiago A Mestre, Jennifer Panagoulias, Christopher A Ross, Maurice Zauderer, Ariana P Mullin, Klaus Romero, Sudhir Sivakumaran, Emily C Turner, Jeffrey D Long, Cristina Sampaio, on behalf of the Huntington's Disease Regulatory Science Consortium (HD-RSC)†*

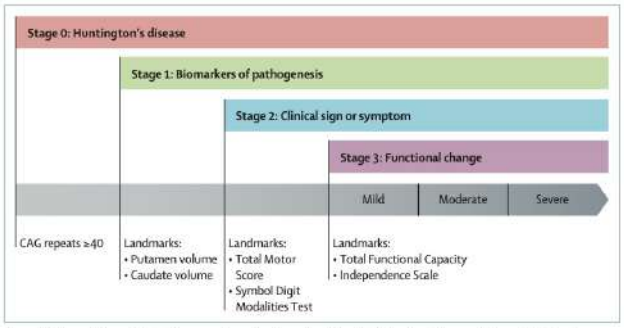
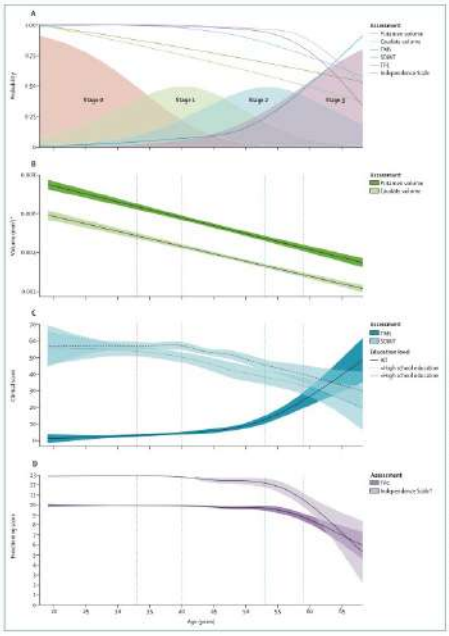
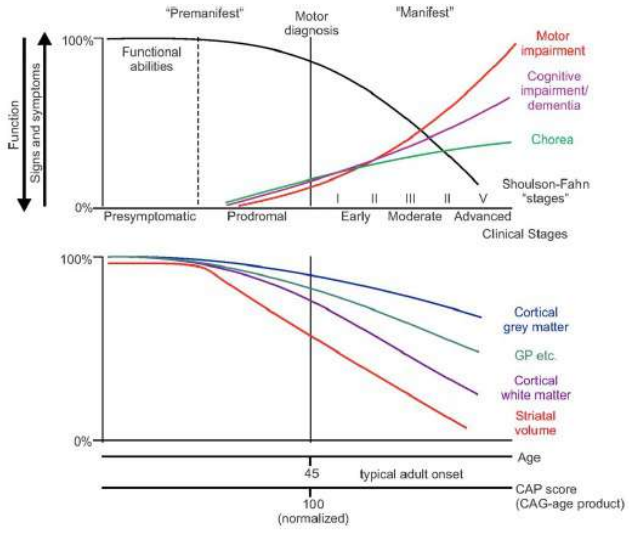


***Figure 3*: Cumulative staging framework and landmarks of the Huntington's disease Integrated Staging System**
Representation of the temporal sequence of stage progression and the associated landmark assessments that define stage entry (time not to scale).



Tabrizi et al., 2022

Biomarkers



Reilmann et al., 2014;
Abeyasinghe et al., 2021

Biofluid-based biomarkers

- Various blood biomarkers
  - Merits of minimal invasiveness, low cost, easy accessibility and safety
- Neurofilament light chain (NfL)
  - Neuronal marker associated with neurodegeneration
  - Tracks with longitudinal change (blood and CSF)
  - Associated with predicted years to clinical motor diagnosis in HD, including HD-ISS Stage 1, ? utility for enriching grouping
  - NfL > GFAP in preHD and early HD
- CSF studies
  - Strong associations of select CSF proteins with clinical measures of disease severity in manifest HD (C1QB, CNR1, NEFL, PDYN, PPP1R1B, and TTR) and with years to predicted disease onset in premanifest HD mutation carriers (ALB, C4B, CTSD, IGHG1, and TTR)
  - PENK as being the most discriminant CSF protein for stratifying HD mutation carriers from controls
  - Combinations of CSF proteins outperform individual markers for stratifying individuals based on HD mutation status and disease severity

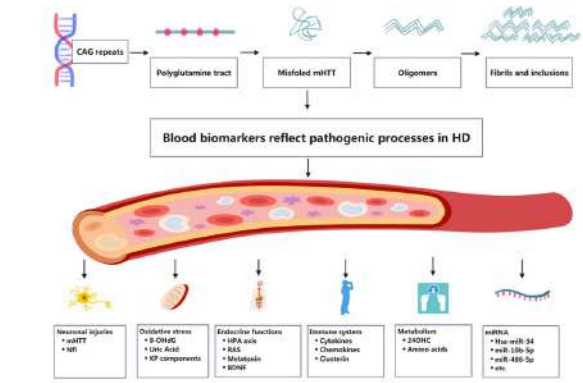
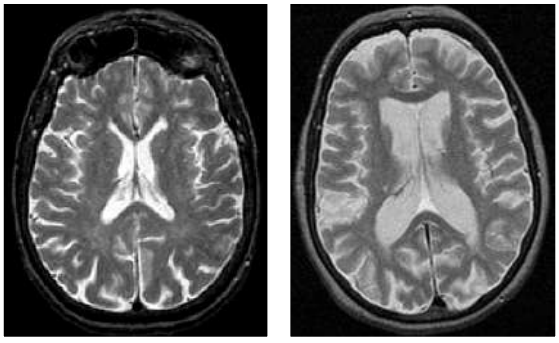


Fig. 1 The current understanding of pathogenesis underlying HD and its related blood-based biochemical biomarkers

Byrne et al., 2017; Caron et al., 2022; Zhang et al., 2023; Sampaio et al., 2023; Parkin et al., 2023; Heim et al., 2025

Imaging



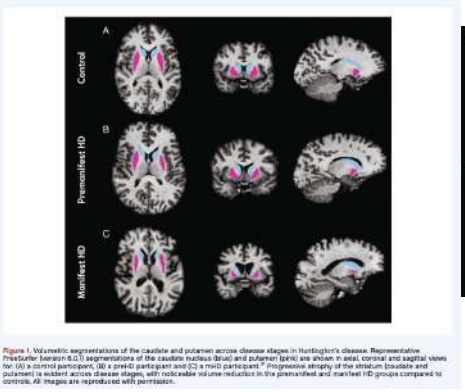
- Striatal atrophy
  - Putamen and caudate volumes
- Cortical thinning
- White matter atrophy
- DTI changes

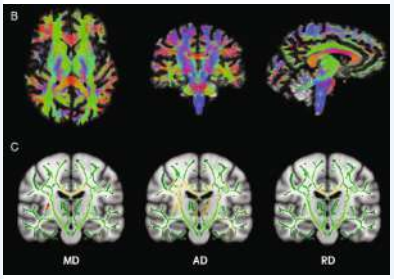
- Microglial 11C-PK11195 – increased binding
- Phosphodiesterase 10A (PDE10A) changes

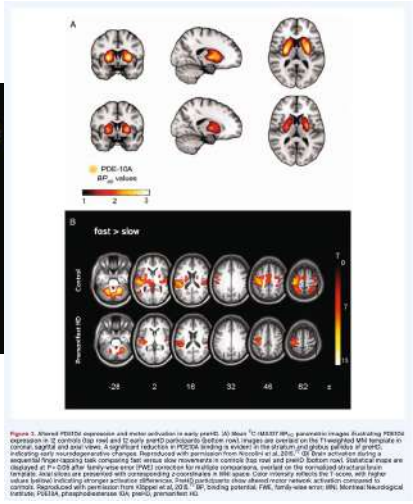
Tabrizi et al., 2011; Niccolini 2014; Aylward 2014; Paulsen et al., 2014; Wilkes et al., 2019

Neuroimaging Techniques in Huntington's Disease: A Critical Review

Mena Farag, MBBS, MRCP,[1] Harry Knights, MBBS, MRCP,[1] Rachael I. Scahill, MA, MSc, PhD,[1] Peter McColgan, MB BCh BAO, MRCP, PhD,[1,2] and Carlos Estevez-Fraga, MD, PhD[3,4]



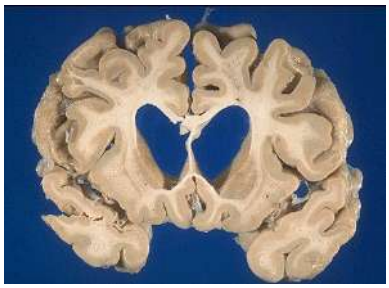




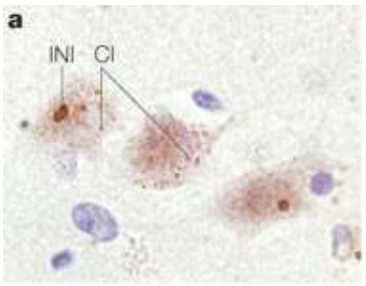
Farag et al., 2025

Pathology

- Striatal atrophy with neuronal loss and gliosis
- Caudate > putamen atrophy
  - "Box car" ventricles
- Marked neuronal loss in deep layers of cerebral cortex, and other basal ganglia, thalamus, cerebellum, to varying degrees



- Affects mediolateral, dorsoventral gradients
  - Input to GPe/SNr before Gpi
- Medium spiny neurons
- Nuclear (INI) and cytoplasmic inclusions (CI) of huntingtin



Ross and Pourier 2005

HD and tau

- Evidence of greater binding of tau-PET, tau in brain tissue, tau inclusions in fetal transplanted HD tissue, higher CSF tau but with variable correlations to clinical measures
- Elevated CSF tau levels in HD patients, correlate with motor dysfunction, cognitive decline, disease burdn
- Conflicting results regarding association with UHDRS TMS

- 23 HD mutation carriers – elevated skin tau levels in manifest HD compared with premanifest and healthy controls
- Correlated with CAG repeat length, CAP score, cUHDRS TMS, cognitive tests, brain atrophy

Gratuze et al., 2016; Salem et al., 2023, 2024; Mees et al., 2023: Lepinay et al., 2023; Owen et al., 2025; Ruiz-Barrio et al., 2025

Tau: a biomarker of Huntington's disease

Eva Lepinay[1,2] and Francesca Cicchetti[1,2]

Evidence of mutant huntingtin and tau-related pathology within neuronal grafts in Huntington's disease cases

Shireen Salem, Mitchell D. Kilgore, Mehwish Anwer, Alexander Maxan, Dan Child, Thomas D. Bird, C. Dirk Keene, Francesca Cicchetti, Caitlin Latimer

Skin Tau Quantification as a Novel Biomarker in Huntington's Disease

CME

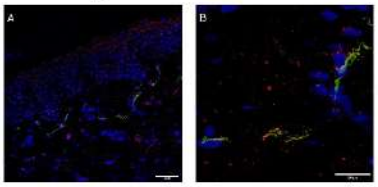


FIG. 1. Confocal microscopy image of a skin section from a Huntington's disease mutation carrier. (A) Colocalization (yellow) between Protein Gene Product (PGP) 9.5 (green) and total tau (red) at nerves located at the dermoepidermal junction. Original magnification: ×40. Scale bar = 50 μm. (B) Nerve bundle amplification with tau colocalization (yellow). Original magnification: ×63; zoom: ×2. Scale bar = 25 μm. [Color figure can be viewed at

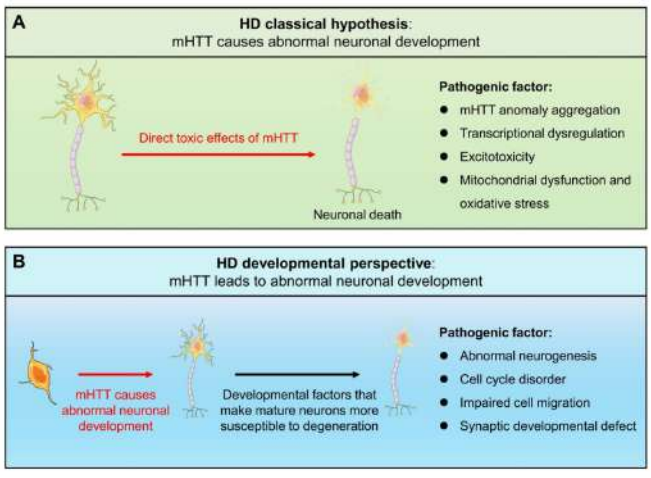
Neurodevelopmental?



Exploring huntington's disease from a neurodevelopmental perspective

Chunhui Huang[1,4], Xiao Zheng[1,4], Wei Li[1], Zaijun Zhang[1,2], Shihua Li[1], Xiao-Jiang Li[3], Mingdeng Rong[1,2], Sen Yan[1,4,5]

- HTT is critical in early embryonic development before emergence of the nervous system
- HTT plays a key role in multiple stages of neurogenesis, including proliferation and differentiation of neural stem cells, neuronal migration, and synapse formation



Huang et al., 2026

Management

- Genetic counseling
- Symptomatic treatment
  - Motor
  - Psychiatric
  - Cognitive
  - Dysarthria
  - Nutrition, weight loss
  - Dysphagia
- Psychosocial
- Disease-modifying?

International Guidelines for the Treatment of Huntington's Disease

Anne-Catherine Bachoud-Lévi[1*], Joaquim Ferreira[2], Renaud Massart[1], Katia Youssov[1], Anne Rosser[3], Monica Busse[4], David Craufurd[5,6], Ralf Reilmann[7,8], Giuseppe De Michele[9], Daniela Rae[10], Ferdinando Squitieri[11], Klaus Seppi[12], Charles Perrins[13], Clarisse Scherer-Gagou[14], Olivier Audrey[14], Christophe Verny[15] and Jean-Marc Burgunder[16]

Symptomatic treatment options for Huntington's disease (guidelines of the German Neurological Society)

Carsten Saft[1*], Jean-Marc Burgunder[2], Matthias Dose[3], Hans Heinrich Jung[4], Regina Katzenschlager[5], Josef Priller[6,7], Huu Phuc Nguyen[8], Kathrin Reetz[9], Ralf Reilmann[10,11,12], Klaus Seppi[13] and Georg Bernhard Landwehrmeyer[14]

Bachoud-Levi et al., 2019; Saft et al., 2023

Genetic counseling

- Important role
- Understanding what HD is and means for families
- Predictive testing
- Confirmatory and diagnostic testing
- Absent family history
- Atypical symptoms
- Reproductive decision-making

Predictive genetic testing for Huntington's disease: Exploring participant experiences of uncertainty and ambivalence between clinic appointments

L. M. Ballard[1] | S. Doheny[2] | R. Dimond[3] | A. M. Lucassen[1,4] | A. J. Clarke[2]

Narrative therapy and family therapy in genetic counseling: A scoping review

Aimee Dane[1] | Jennifer Berkman[2] | Emily DeBortoli[2] | Courtney K. Wallingford[2] | Tatiane Yanes[2] | Aideen McInerney-Leo[2]

Ballard et al., 2024; Dane et al, 2024

An MDS Evidence-Based Review on Treatments for Huntington's Disease

Joaquim J. Ferreira, MD, PhD,[1,2,3*] Filipe B. Rodrigues, MD, MSc,[2,3,4] Gonçalo S. Duarte, MD, MSc,[1,2,5,6] Tiago A. Mestre, MD, PhD,[7] Anne-Catherine Bachoud-Levi, MD,[8,9,10] Anna Rita Bentivoglio, MD, PhD,[11,12] Jean-Marc Burgunder, MD,[13,14] Francisco Cardoso, MD,[15] Daniel O. Claassen, MD, MS,[16] G. Bernard Landwehrmeyer, MD,[17] Jaime Kulisevsky, MD, PhD,[18,19,20] Melissa J. Nirenberg, MD, PhD,[21] Anne Rosser, PhD, FRCP,[22] Jan Roth, MD, PhD,[23] Klaus Seppi, MD,[24] Jaroslaw Slawek, MD, PhD,[25,26] Erin Furr-Stimming, MD,[27] Sarah J. Tabrizi, MD, PhD,[4,28,29] Francis O. Walker, MD,[30] Wim Vandenberghe, MD, PhD,[31,32] João Costa, MD, PhD,[1,2,5] and Cristina Sampaio, MD, PhD[2,33]

- Results: Twenty-two eligible studies involving 17 interventions were included, providing data to address 8 clinical questions.
- These data supported a likely effect of deutetrabenazine on motor impairment, chorea, and dystonia and of tetrabenazine on chorea.
- The data did not support a disease-modifying effect for premanifest and manifest HD.
- There was no eligible evidence to support the use of specific treatments for depression, psychosis, irritability, apathy, or suicidality. Similarly, no evidence was eligible to support the use of physiotherapy, occupational therapy, exercise, dietary, or surgical treatments.
- Conclusions: Data for therapeutic interventions in HD are limited and support only the use of VMAT2 inhibitors for specific motor symptoms.

Ferreira et al., 2022

Chorea

- Tetrabenazine (VMAT2 inhibitor; FDA 2008)
- Deutetrabenazine (VMAT2 inhibitor = deuterated analogue of TBZ, FDA 2017)
- Valbenazine (VMAT2 inhibitor; valine-ester prodrug of active DEU metabolite, FDA 2023)
- Neuroleptics
- Amantadine (evidence +/-)

- Riluzole (RCT - NS)
- DBS (palliative)
- Rehab therapies/safety
- Note, side effects and dosing

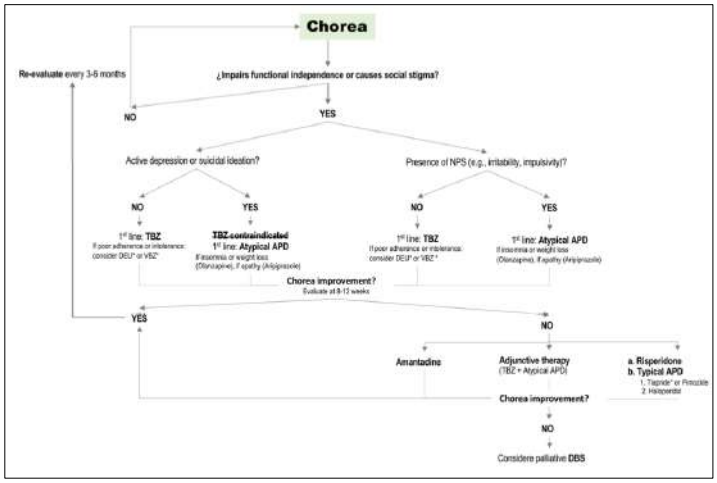
Mechanism	Drug Name	Recommended Starting Dose	Recommended Maximal Dose	Availability	Estimated Price
VMAT 2 INHIBITORS	Tetrabenazine (TBZ)	12.5–25 mg (QD or BID)	*,† 75 mg/d (TID)	Worldwide	Low–moderate
	Deutetrabenazine (DEU)	12 mg (BID)	* 48 mg/d (BID)	USA, Canada, Australia, selected European countries	High
	Valbenazine (VBZ)	40 mg (QD)	* 80 mg/d (QD)	USA	High
ATYPICAL APDs	Olanzapine	2.5–5 mg (QD or BID)	20 mg/d (BID)	Worldwide	Low–moderate
	Aripiprazole	2–15 mg (QD or BID)	30 mg/d (BID)	Worldwide	Low–moderate
	Risperidone	0.5–2 mg (QD or BID)	16 mg/d (BID)	Worldwide	Low
TYPICAL APDs	Tiapride	50–200 mg (QD or BID)	900 mg/d (TID)	Europe	Low
	Pimozide	1 mg (QD)	2–4 mg/d (QD)	Worldwide (limited availability)	Low
	Haloperidol	0.5–2 mg (QD or BID)	10 mg/d (BID)	Worldwide	Low
NMDA ANTAGONIST RECEPTOR	Amantadine	100–200 mg (QD or BID)	400 mg (BID)	Worldwide	Low

Frank 2014; Olmedo-Saura et al., 2025

Chorea

Table 3 Considerations when treating chorea pharmacologically

If the patient has troublesome chorea with:	Consider using:
No other symptoms	Tetrabenazine, amantadine, (riluzole)
Weight loss	Olanzapine, cannibinoids
Psychosis, aggression or impulsivity	Aripiprazole, haloperidol, olanzapine, risperidone, or other neuroleptic
Anxiety	Benzodiazepines
Depression	Aripiprazole and avoid tetrabenazine
Apathy	Amantadine or stimulating medications and avoid neuroleptics
Prominent dystonia	Amantadine, benzodiazepines, focal neurotoxin injection, and avoid neuroleptics
No response to pharmacotherapy	Deep brain stimulation



Frank 2014; Olmedo-Saura et al., 2025

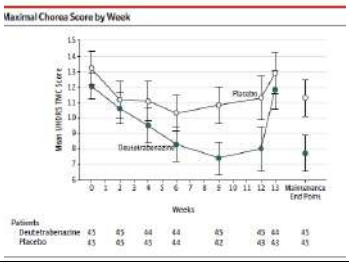
Original Investigation

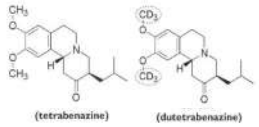
Effect of Deutetrabenazine on Chorea Among Patients With Huntington Disease

A Randomized Clinical Trial

Huntington Study Group 2016

- N=90, manifest HD patients
- DTBZ (n = 45) or placebo (n = 45)
- Titrated over 8 weeks, 4-week maintenance, 1 week washout
- Primary endpoint: Δ from baseline in total maximal chorea score
- Improved total maximal chorea score 4.4 units DTBZ vs. 1.9 units placebo; mean between group difference -2.5 units (p<0.001)
- Significant improvement in patient global impression of change
- AEs –depression, anxiety, akathisia (both groups)





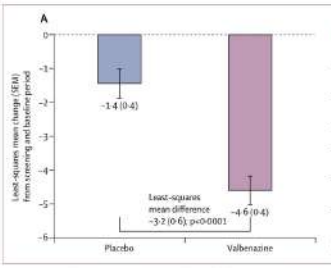
- FDA approved in 2017
- Long-term study (ARC-HD) efficacy and safety, ≥1 year follow up (mean 119 +/- weeks)
- Open label extension (3 yr) – consistent with prior studies for AEs and effects on chorea
- Post-hoc analysis of ARC-HD open-label, long-term study, higher doses of DTBZ > 48 mg/d did not produce any new safety concerns or incremental change in the safety profile between dosages of ≤48 mg/d and > 48 mg/d.

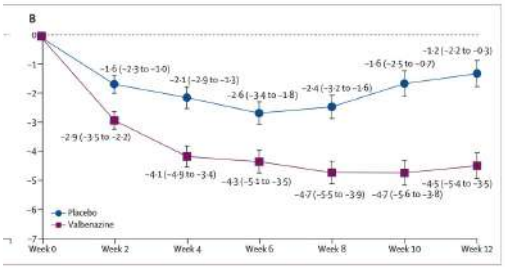
HSG 2016; Frank et al., 2021; Frank et al., 2022, 2024. 2025

Safety and efficacy of valbenazine for the treatment of chorea associated with Huntington's disease (KINECT-HD): a phase 3, randomised, double-blind, placebo-controlled trial

Erin Furr Stimming, Daniel O Claassen, Elise Kayson, Jody Goldstein, Raja Mehanna, Hui Zhang, Grace S Liang, Dietrich Haubenberger, on behalf of the Huntington Study Group KINECT-HD Collaborators*

- Valbenazine - highly selective VMAT2 inhibitor, approved for tardive dyskinesia
- RCT, DB-PC, Phase 3 study - KINECT-HD (NCT04102579), multicenter, 12 weeks
- Primary endpoint - change in UHDRS TMC score
- 125 HD patients
- Least-squares mean changes from the screening and baseline period to the maintenance period in the UHDRS TMC score were –4·6 for valbenazine and –1·4 for placebo (least-squares mean difference –3·2, 95% CI –4·4 to –2·0; p<0·0001)
- Most commonly reported treatment-emergent AE somnolence
- No suicidal behavior or worsening of suicidal ideation
- FDA approved in 2023 for chorea of HD





Furr Stimming et al., 2023

Other symptoms and management to consider

Motor Symptom	Special Considerations	Pharmacological Interventions	Non-Pharmacological Interventions
MOTOR IMPERSISTENCE	May be highly disabling.	No approved therapies. Empirical use of TBZ, amantadine, or APD (especially when coexists with chorea).	No specific evidence available; physiotherapy and task-specific motor training may help.
DYSTONIA	Often mild and action-induced; specific pharmacological treatment is rarely needed. • Severe or fixed forms are frequent in JHD.	First step: reduce antidopaminergic medication if present. Second step: Same management as for idiopathic dystonias. • JHD: Intrathecal baclofen or GPi/STN-DBS in refractory cases.	Active/passive physiotherapy, stretching, and postural re-education.
PARKINSONISM	Typically emerges in late-stage or as drug-induced; specific pharmacological treatment is rarely needed. • Prominent and disabling in JHD.	First step: reduce antidopaminergic medication if present. Step step: consider levodopa or amantadine (especially if chorea coexists).	Same as for dystonia.
GAIT DISTURBANCES	Multifactorial origin; not solely attributable to chorea.	No approved therapies. Treat contributing factors (e.g., chorea, dystonia, motor impersistence) if present and functionally impairing.	Specialized physiotherapy, postural training, proprioceptive strategies, and early use of assistive devices (e.g., walker, wheelchair).
AKATHISIA	Mostly iatrogenic (TBZ, APD or SSRIs)	First step: identify and reduce or withdraw causative agent. Alternatives: Beta-blockers, BZD.	No specific evidence available; management is primarily pharmacological.
MYOCLONUS	Treatment only required if functionally disabling. • Common in JHD.	First step: LEV, CZP Alternatives: VPA	No specific evidence available; management is primarily pharmacological.
TICS	Specific treatment is rarely needed.	Usually managed similarly to chorea.	If intervention is required, follow TS management principles: behavioral therapy (CBT/habit reversal), education, reassurance.
DYSPHAGIA	Clinically significant in advanced stages. Early discussions about PEG placement are essential to align care with patient prefererences.	Consider treating contributing factors (e.g., pharyngeal chorea or tics).	Regular swallowing evaluations by specialists; caregiver training to detect early signs; dietary texture modifications; PEG when indicated.
WEIGHT LOSS	Highly prevalent and multifactorial.	High-calorie, high-protein nutritional supplementation. Consider H1 antagonist agents particularly when weight loss is associated with chorea (e.g., olanzapine), or with depression or insomnia (e.g., mirtazapine).	Regular nutritional assessment.

Frank 2014; Olmedo-Saura et al., 2025

Movement Disorders
CLINICAL PRACTICE
REVIEW

Pharmacological Treatment of Neuropsychiatric Symptoms in Huntington's Disease: A Systematic Review

Ruben L. Andriessen, MD,[1,2]* Mayke Oosterloo, MD, PhD,[1,2] Jory Molenaa, MD,[1] Maud M.J. Doornen, MS,[2,3] David E.J. Linden, MD, DPhil,[1,2,3] and Albert F.G. Leentjens, MD, PhD[2,3]

ABSTRACT: **Background:** Studies focusing on the treatment of neuropsychiatric symptoms (NPS) in Huntington's disease (HD) are scarce and show a wide variation in design, outcome measures and methodological quality. The effectiveness of pharmacological treatment of NPS in HD has not been systematically reviewed so far.
Objective: To provide an overview of the available literature on the effectiveness of pharmacological treatment of NPS in HD.
Methods: PubMed and the Cochrane library were systematically searched for studies assessing the effects of pharmacotherapy of NPS, both as a primary and as secondary outcome. A risk of bias assessment was performed for each article.
Results: Fifteen articles qualified for critical evaluation: 10 randomized controlled trials (RCTs) (five placebo-controlled and five cross-over) and five open label studies. One RCT reported improvement of the overall NPS with nabilone treatment; another RCT reported that fluoxetine slightly improved irritability. Lower-level evidence from open studies suggests that the atypical antipsychotics cariprazine, olanzapine and risperidone may improve overall NPS, and that cariprazine, venlafaxine XR and olanzapine may improve depression. In addition, olanzapine may improve obsessive thoughts, aggression, anxiety and irritability.
Conclusions: We conclude that although NPS in HD are common, hardly any clinical trials have addressed their treatment. As a result, convincing evidence that could guide clinical practice is lacking. More focused, and larger, multicenter trials focusing on NPS are urgently needed to generate the knowledge necessary to support the development of evidence-based clinical treatment guidelines.

TABLE 2 *Symptom-specific scales*

Neuropsychiatric symptom*	Assessment scale
Depressed mood	Beck Depression Inventory (BDI) Hospital Anxiety and Depression Scale (HADS) Hamilton Rating Scale for Depression (HAM-D) NPI depression section UHDRS behavioral domain depression items
Suicidal ideation	Columbia Suicide Severity Rating Scale (C-SSRS) UHDRS behavioral domain suicidal thoughts items
Anxiety	Zung Anxiety Scale UHDRS behavioral domain anxiety items
Irritability	Smith Irritability Scale (SIS) Comprehensive Behavior Rating Scale-agitation (CBRS-agitation) NPI irritability section UHDRS behavioral domain irritability items
Angry or aggressive behavior	UHDRS behavioral domain aggression items
Apathy	Structured Clinical Interview for Apathy-dementia (SCIA-D) Apathy Evaluation Scale (AES) Problem Behavior Assessment-shortform (PBA-s) Positive and Negative affect schedule (PANAS) NPI apathy section UHDRS behavioral domain apathy items
Obsessive behavior	Leyton Obsessional Inventory (LOI) UHDRS behavioral domain obsession items
Compulsive behavior	UHDRS behavioral domain compulsion items
Delusions/paranoid thinking	UHDRS behavioral domain delusion items
Hallucinations	UHDRS behavioral domain hallucination items
Cognitive functions	Addenbrooke Cognitive Examination (ACE) Mini-Mental State Examination (MMSE) Connors' Adult ADHD Rating Scale (CAARS) UHDRS cognitive domain score Separate analysis of cognitive tests[b]
Composite scores	UHDRS behavioral NPI Symptom Checklist-R-90-R (SCL-R-90-R)

Andriessen et al., 2025

Mood: depression and anxiety

- Environmental changes
- SSRI's or SNRI's
- Antipsychotics
- Mood stabilizers

- *Systematic review*
- *RCTs (cross-over studies)*
  - *Buproprion (p=0.07), fluoxetine (p=0.06), citalopram (NS)*
  - *Fluoxetine (anxiety, p=0.07)*
- *Open label studies*
  - *Cariprazine (p=0.097), venlafaxine XR (p<0.001), olanzapine (p=0.013)*
  - *Olanzapine (anxiety, o=0.016)*

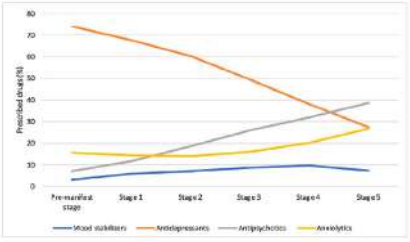


Fig. 2. Rates of prescriptions for neuropsychiatric indications of various drug classes across advancing disease stages of HD. A colored version of this figure

- Prescription rates (Enroll-HD)
- Of the 8967 included (pre)manifest HD, 80% taking at least one psychotropic drug and 63% using psychotropic drugs for neuropsychiatric indications
  - 55.4% antidepressant, 37.6% antipsychotic, 27.1% anxiolytic drug, 9.6% mood stabilizer

Ogilvie et al., 2022; Andriessen et al., 2025

Behavior

- Irritability or aggressive behavior
  - Environmental changes
  - Antipsychotics
  - SSRI's or SNRI's
  - Mood stabilizers
- *Systematic review*
  - *RCTs (cross-over studies)*
    - *Fluoxetine (p=0.02); buproprion (NS) - irritability*
  - *Open label studies*
    - *Olanzapine (irritability, p=0.047 and aggression NS)*
- SRX246, first in-class vasopression 1a (V1a) receptor antagonist
  - Safe and well tolerated (Maibach et al., 2022)
- Apathy
  - Variable but SSRI's or SNRI's, cognitive meds
  - Environmental stimulation, activities
- OCD
  - SSRI's
- Delusions/paranoid thinking
  - Antipsychotics
- *Systematic review*
  - *RCTs (cross-over studies)*
    - *Buproprion (apathy, NS), modafinil (apathy, NS)*
    - *Fluoxetine (OCD, NS)*
  - *Open label studies*
    - *Olanzapine (obsessions, p=0.048; delusions, p=0.085)*

Frank 2014; Moulton et al., 2014; Brownstein et al., 2020; Maibach et al., 2022; Andriessen et al., 2022;2025; Theleritis et al., 2023

Cognitive impairment

- Cholinesterase inhibitors
  - Donepezil: randomized, placebo-controlled study (n=30) —> no benefit for cognition, chorea or QoL
  - Rivastigmine: randomized, placebo-controlled, parallel study (n=18) —> no benefit for MCI
- Memantine
  - Open label, n=12, UHDRS, 3 mos, no benefit (20 mg/d)
  - Enroll-HD, trajectories of cognition over 5-years in memantine users → no difference between treated vs untreated
- Non-pharmacological
  - Adaptations at work/home
  - Cognitive-behavioral strategies
  - Systematic review
    - 17 studies (3 cog, 7 exercise, 7 cog + exercise)
    - Low evidence but cog training larger effect size on cognition, while physical exercise had negligible effect sizes
- *Systematic review*
  - *RCTs (cross-over studies)*
    - *Citalopram (NS), latrepirdine (2 studies: p=0.03 and NS), fluoxetine (NS)*
  - *Open label studies*
    - *Cariprazine (sig), risperidone (worsening)*

Cubo et al., 2006; Ondo et al., 2007; Sesok et al., 2014; Ogilvie et al., 2023; Huynh et al., 2023; Koenig et al., 2024; Andriessen et al., 2025

Neuropsychiatric symptoms (summary)

NPS	Special Considerations	Pharmacological Interventions	Non-Pharmacological Interventions
DEPRESSION	Treatment should be tailored to coexisting symptoms (e.g., irritability, apathy, insomnia).	First step: SSRIs (sertraline, citalopram) or SNRIs (venlafaxine, duloxetine). In severe or recurrent cases: consider mood stabilizers (VPA, CBZ, LTG).	Psychotherapy and/or CBT. Consider ECT in selected treatment-resistant cases.
ANXIETY	May be exacerbated by comorbidities or medications.	First step: address comorbid conditions. Second step: SSRIs or SNRIs • Consider BZD for acute anxiety episodes or during SSRI/SNRI titration.	Structured routines, relaxation techniques, psychoeducation (for patients and caregivers).
APATHY	One of the most disabling and underrecognized NPS.	**No approved therapies.** First step: review and reduce potentially aggravating medications. Second step: Consider SSRIs (if depression is present), or activating agents (methylphenidate, modafinil).	Structured daily routines, and tailor social or physical activities to enhance motivation.

NPS	Special Considerations	Pharmacological Interventions	Non-Pharmacological Interventions
IRRITABILITY AND AGGRESSIVENESS	Treatment should be guided by symptom severity and coexisting psychiatric features.	First step: High-dose SSRIs (sertraline and escitalopram). Second step: APD (aripiprazole or olanzapine). Consider adjunctive mood stabilizers in refractory cases.	Behavioral strategies: avoid confrontation, de-escalate early signs, and use distraction techniques.
PERSEVERATIVE IDEATION AND OCD	Perseveration is much more common.	Perseveration: SSRIs or APD (olanzapine or risperidone). OCD: High-dose SSRIs or clomipramine.	CBT and psychoeducation (for patients and caregivers).
PSYCHOSIS	Important to rule out and treat comorbid medical conditions that may trigger or worsen psychosis.	First step: APD (olanzapine, risperidone or aripiprazole). If no response, consider other APDs such as clozapine.	Consider ECT in severe treatment-resistant cases.
SUICIDAL IDEATION	**Suicide risk should be systematically assessed.** May occur independently of major depression.	First step: Prompt identification and management of contributing factors (depression, impulsivity or perseveration) or withdraw possible contributing medications (e.g., TBZ) Second step: Consider APD (olanzapine)	Ensure caregiver involvement, prevent social isolation. Consider psychiatric hospitalization if safety is compromised.
IMPULSIVITY	Treatment should be tailored to symptom profile.	If comorbid depression or irritability: SSRIs. If impulsive aggressivity: atypical APD. Consider adjunctive mood stabilizers.	Psychoeducation (for patients and caregivers) to provide insight and reduce triggers.

Olmedo-Saura et al., 2025

Clinical recommendations to guide physical therapy practice for Huntington disease

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Abstract

Objective
In the past decade, an increasing number of studies have examined the efficacy of physical therapy interventions in people with Huntington disease (HD).

Methods
We performed a mixed-methods systematic review using Joanna Briggs Institute (JBI) methodology and included experimental and observational study designs. The search resulted in 23 quantitative studies and 3 qualitative studies from which we extracted data using JBI standardized extraction tools. Results of this review suggested that physical therapy interventions may improve motor impairments and activity limitations in people with HD. Here, we expand on the review findings to provide specific recommendations to guide clinical practice.

Results
We recommend the following specific physical therapy interventions for people with HD: aerobic exercise (grade A evidence), alone or in combination with resistance training to improve fitness and motor function, and supervised gait training (grade A evidence) to improve spatiotemporal features of gait. In addition, there is weak (grade B) evidence that exercise training improves balance but does not show a reduction in the frequency of falls; inspiratory and expiratory training improves breathing function and capacity; and training of transfers, getting up from the floor, and providing strategies to caregivers for involvement in physical activity in the midstages of HD may improve performance. There is expert consensus for the use of positioning devices, seating adaptations, and caregiver training in late stages of HD.

Conclusions
There is strong evidence to support physical therapy interventions to improve fitness, motor function, and gait in persons with HD.

Aerobic exercise +/- resistance training
Supervised gait training

Update of Rehabilitation in Huntington's Disease: Narrative Review

Ki-Hong Kim,[1] Min-Keun Song[2,3]

Table 1. Rehabilitation management strategies according to the stage of Huntington's disease

Variables	Early stage	Middle stage	Late stage
Exercise performance	· Aerobic and resistance exercises (moderate intensity within 50%–70% of maximal heart rate, three times per week for 12 wk)		
Mobility and gait	· Task-specific mobility, training focused on individual gait function	· Task-specific mobility training	
Postural control, alignment in sitting, balance and fall risk		· Fall risk assessment · Proper positioning for mobility · Seating and wheelchair evaluation · Balance and gait training (moderate frequency and intensity)	· Fall risk assessment · Seating and wheelchair evaluation · Proper timed sit positioning
Secondary musculoskeletal changes and deconditioning	· Education for patient to maintain exercise program, gait, and balance	· Education for patient and caregiver to maintain exercise program, gait, and balance	
Planning and performing of tasks for movement	· Task-specific training (strategy training, sensory stimulation, cueing, and chaining)	· Task-specific therapy (strategy training, sensory stimulation, cueing and chaining, occupational therapy)	
Cognitive training	· Multidisciplinary rehabilitation for cognition	· Multidisciplinary rehabilitation for cognition	
Psychological management	· Multimodal daycare rehabilitation	· Multimodal daycare rehabilitation	
Respiratory exercise		· Positioning · Inspiratory and expiratory breathing training · Airway clearance methods · Respiratory muscle relaxation techniques	· Inspiratory and expiratory breathing training · Airway clearance method, especially coughing
Physical exercise to prevent complications in patients with severely impaired mobility			· Bed positioning · Passive range of motion · Active movement exercises

Quinn et al., 2020, PACE-HD 2022; Kim et al., 2023

Multidisciplinary care for HD

What we don't need to prove but need to do in multidisciplinary treatment and care in Huntington's disease: a position paper

Alzbeta Mühlbäck[1,2,3], Marleen van Walsem[4,5], Martha Nance[6,7], Astri Arnesen[8], Kirsty Page[9], Alexandra Fisher[10], Manon van Kampen[11], Angela Nuzzi[12], Roy Limpert[2], Hanne Ludt Fossmo[13,14], Travis Cruickshank[15] and Ruth Veenhuizen[11,16,17]* on behalf of the Multidisciplinary Care and Treatment Working Group of the European Huntington's Disease Network

Coordination of Care Among Physical Therapists and Neurologists in Huntington Disease

Nora E. Fritz, PhD, PT, DPT, NCS, Deb Kegelmeyer, MS, PT, DPT, GCS, Ashwini K. Rao, EdD, OTR/L, FAOTA, Lori Quinn, EdD, PT, Martha A. Nance, MD, and Anne Kloos, PhD, PT, NCS

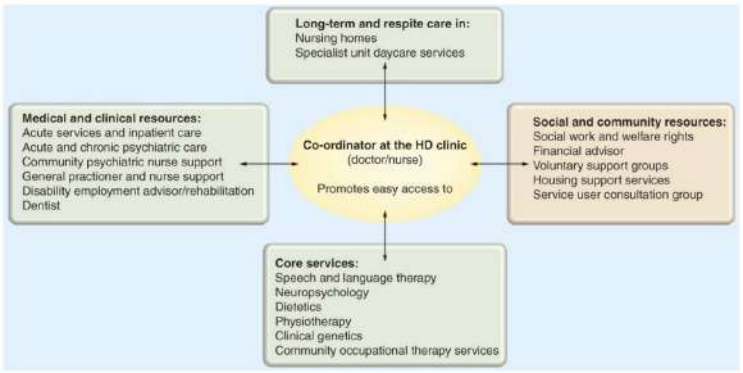


Fig. 1 Concept of the managed care network in HD in which the coordinator is the central person for the family and the whole network

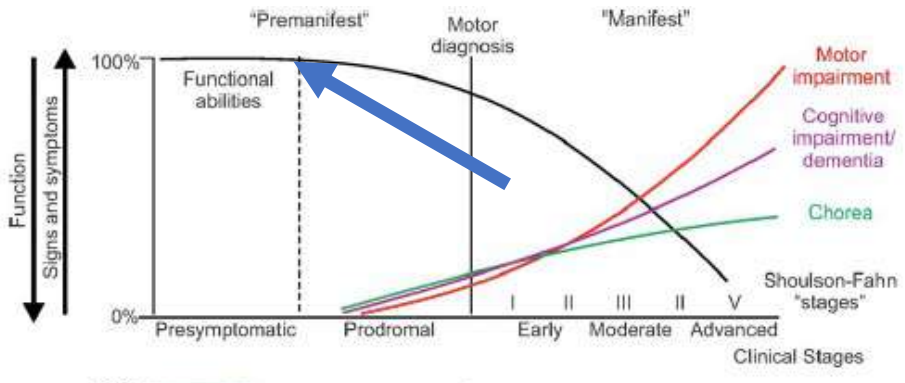
Mühlbäck et al., 2023; Fritz et al., 2022; Seeberger et al., 2022

Palliative and advanced care planning

- Physical care
- Psychological care
- Social care
- Spiritual care
- Advance care planning
- End-of-life needs assessments

Boersema-Aijma et al., 2023; Farag et al., 2023; Sokol et al., 2023; Harrison et al., 2022

Disease-modifying?



Negative results

- Coenzyme Q10
  - Early-stage HD, n=609, 60 months → no change TFC; safe and well-tolerated (McGarry et al., 2017)
- Creatine
  - Early manifest HD, n=553, 48 months → halted, no effect on TFC; GI side effects (Hersch et al., 2018)
- VX15/2503 – pepinemab
  - Late prodromal/early manifest HD, n=265, 18 months → NS in HD cog or CGIC, promising neuroimaging data? (Feigen et al., 2022)
- Laquinimod
  - Early manifest HD, n=352, 12 months → NS on UHDRS-Total motor score; reduced caudate volume loss (Reilmann et al., 2024)

The pridopidine journey

- Pridopidine - "Dopamine stabilizers"
  - HART (North America, n=227)
    - Modified motor score (not significant)
  - MermaiHD (Europe, n=437)
    - Modified motor score (trend) but significant improvements global motor score, eye movements, dystonia, hand movements, gait/balance
  - PRIDE-HD (n=400)
    - Higher doses, longer study, additional outcome
    - Improved TFC but no difference from placebo on total motor score
    - At the 45 mg bid therapeutic dose, pridopidine had a favorable cardiac safety profile, with effect on QTc interval below the level of concern and not clinically relevant (Darpo et al., 2023)
  - Prilenia PROOF HD (ongoing)
    - Phase 3, early stage HD, recruitment completed (n=499)
    - Primary endpoint TFC not met
    - Excluding those on anti-DA, improvement in cUHDRS in drug group at week 52, sustained week 78, also improved Q-motor and Stroop Word Reading

Feigin A. Clinical Trials Plenary Session—The Phase 3 PROOF-HD Trial Demonstrates Meaningful Benefits of Pridopidine on Function, Cognition, and Motor Signs in HD. AAN April 2025

- Pridopidine showed significant benefits in HD patients not on anti-DA meds (ADM), improving clinical progression, cognition, and motor function over two years.
- Placebo patients on ADMs had worse outcomes vs. those not on ADMs
- Clinically meaningful improvements were observed in cUHDRS and other cognitive and motor scales for patients on pridopidine without ADMs
- Pridopidine's safety and tolerability were comparable to placebo, with positive effects maintained at lower ADM doses



Dear HD Community,

We would like to share an update on the confirmatory PRECISE-HD study (Pridopidine Phase 3 Study to Establish Clinical Impact and Safety in Huntington's Disease (HD)), a global clinical study evaluating the investigational medicine pridopidine in people living with Huntington's disease. The study has now been listed on www.clinicaltrials.gov (NCT07609108).

Enroll 400 early-mid stage HD, 52 week trial followed by OLE
Primary endpoint – combined UHDRS

Waters et al., 2018; Darpo et al., 2023; Feigin et al., 2022

Therapeutic targets

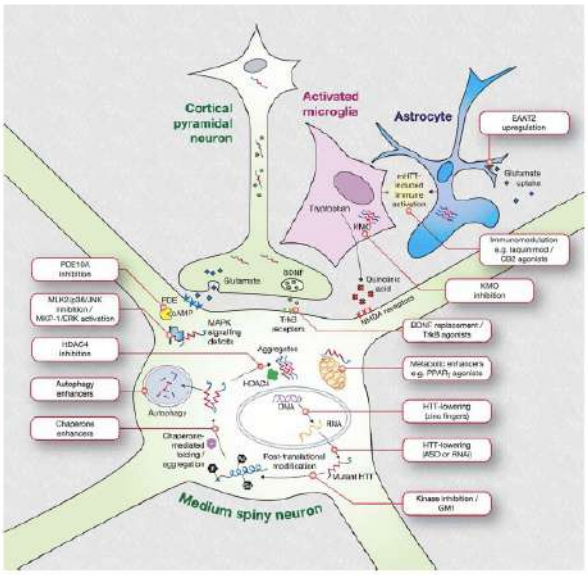
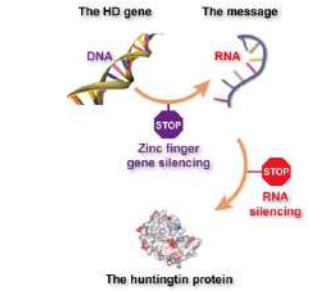
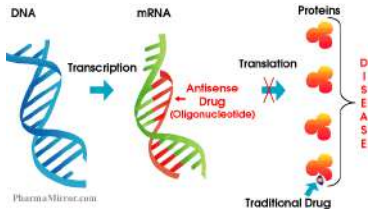


FIG. 1. Schematic depicting current priority preclinical therapeutic targets under investigation for Huntington's disease. HTT, huntingtin; KMO, kynurenine monooxygenase; NMDA, N-methyl-D-aspartate; PDE, phosphodiesterase; BDNF, brain-derived neurotrophic factor; HDAC, histone deacetylase; Trk, tropomyosin-related kinase. Adapted from Ross et al.[96]

Wild and Tabrizi 2014; Ross et al., 2014; Tabrizi et al., 2022

Genetic-therapeutics and HTT-lowering strategies





Active agent	Mode of delivery	Targeted brain region	Stage of development	Other
ASO nonallele-specific	Intrathecal lumbar infusion	Cortex	First in human trial	Do not cross BBB
ASO allele-specific	Intrathecal lumbar infusion	Cortex	Preclinical	SNP-based Do not cross BBB
RNAi	Viral vector Stereo-tactic administration	Basal ganglia (putamen)	Preclinical	
Zinc finger proteins	Viral vector Stereo-tactic administration	Basal ganglia (putamen)	Preclinical	CAG-based

Antisense oligonucleotide drugs


2019

Targeting Huntingtin Expression in Patients with Huntington's Disease

- IONIS-HTTRx
- Phase 1 – Early manifest HD (n=46), IT drug vs. placebo → safety demonstrated, decreased CSF huntingtin

- Phase 3
- GENERATION HD1 – Tominersen vs. placebo, planned manifest HD (n=900) → trial halted March 2021 (n=791) due to lack of benefit, more AEs with more frequent dosing
- GENERATION HD2 – 2 doses of tominersen vs. placebo, prodromal or early manifest HD (n=301) → April 2025 interim pre-planned safety analysis with no concerns, greater clinical benefit with 100 mg dose so stopped 60 mg dose → July 2026 Roche discontinued program – no symptom improvement or disease slowing, did not meet primary endpoint

Tabrizi et al., 2019

WAVE PRECISION-HD1 and -HD2



- Phase 1b/2a Clinical Trials: PRECISION-HD1 and PRECISION-HD2 in HD
- Evaluate the first allele-specific investigational drugs for HD, WVE-120101 and WVE-120102
- Intrathecal
- Early manifest HD with specific SNPs (rs362307 and rs 362331)
- Did not reach significant effects in the brain
- Did not show reach target engagement

- TRIAL HALTED (n=88 participants) – March 2021
  - Did not lower huntingtin protein levels or NfL
  - No significant change in mHTT vs. placebo after single or multiple doses of WVE-120102 and including 32 mg monthly dose
  - No dose response level seen
  - OLE trial (n=28) with modest reductions in mHTT but inconsistent over course of trial → stopped clinical development of WVE-120102

- WVE-003 developed – updated chemical structure/neutral charge for better brain penetration
  - Phase 1b/2a trial
    - Part 1: Early HD and SNP3 mutations, n=47, with doses 30, 60 or 90 mg vs placebo --> tolerability
    - Part 2: Early HD and SNP3 mutations, n=23, with 3 injections of either 30 mg, most well-tolerated dose, or placebo, separated by 8 weeks → mutant htt levels reduced by 46% relative to placebo at 2 months after last injection, also slower caudate nucleus shrinkage
  - Phase 2/3 trial (update July 2026)
    - Designed as a global, potentially registry (pivotal) study
    - Investigation application prepared
    - No sites active yet

UniQure – ups and downs of AMT-130



- Phase I/II, randomized, multicenter, dose escalation, double-blind, imitation surgery, first-in-human study (NCT04120493)
- AMT-130 in early manifest HD
  - Preclinical studies have shown that AMT-130 lowers huntingtin protein and improved HD signs in animal models
- Safety and Proof-of-Concept Study
- Main outcome at 18 months but f/u for 5 years
- Single administration gene therapy for disease-modification
  - Intrastriatal administration rAAV5-miHTT (low dose, high dose) vs. sham surgery
- Reduced mHTT in drug > sham
- Positive interim data – dose-dependent slowing of HD, stabilization of motor and cognitive function, reduced NfL levels

- Sept 2025 – 36 month Phase I/II data – high doses cohorts had 75% slowing of disease progression and decreased NfL
- FDA stipulated that uniQure could not seek immediate accelerated approval based on the open-label dataset.
- Mandated prospective randomized, double-blind, sham surgery controlled Phase III trial
- June 2026 – FDA agreed that existing 3 year clinical data can serve as baseline for a Biologics License Application (BLA) for Q3 2026, keeping the drug on an active tracking pipeline

Recent updates

- Updates June 2026
- PTC PIVOT-HD Phase 2 study of PTC518 (votoplam)
- Oral splicing modulator, non-allele specific
- Study – 5 mg, 10 mg, vs. placebo for 12 months
- Primary endpoint: dose-dependent lowering of mutant huntingtin (mHTT) protein in blood and CSF
- Appears to be safe
- Dose-dependent lowering of mHTT protein through 12 month
- 24 month data, NfL data, brain MRI, clinical readouts – "positive"

- Update June 2026
- SkyHawk SKY-0515, Phase 1 study
- Small molecule, once-daily, oral formulation
- Targets HTT but also somatic expansion, high potency
- Healthy people – safe, well tolerated
- Phase 2/3 FALCON-HD trial to evaluate pharmacodynamics, safety, efficacy in Stage 2 or 3 early HD
- Expanding recruitment

Therapeutic pipeline

Huntington's disease clinical trials update: October 2025

Mena Farag[1], Sarah J Tabrizi[1] and Edward J Wild[1]



Fig. 2. Current pharmaceutical developments in Huntington's therapy- Many pharmaceutical companies are hovering to take the lead for Huntington's disease therapy with their clinical products ranging from small-molecule inhibitors, antisense oligonucleotides, micro-RNA, splicing modulators, stem cells, monoclonal antibodies, and dietary supplements. Here, Lundbeck and Teva pharmaceuticals possess clinically approved medicine for symptomatic treatment of HD. While Neurocrine biosciences and Prilenia therapeutics are leading in the clinical phase 3 trials for treating chorea in HD patients, Azidus is undergoing clinical phase 3 testing for mesenchymal stem cell therapy for HD in case of disease-modifying therapies. However, other companies, including Wave life sciences, Uniqure, Novartis, and Annexon biosciences, are currently leading the disease-modifying HD therapeutic research in clinical phase 2 testing of antisense oligonucleotides micro-RNA, and splice modulators. **DRP1**- Dynamin-related protein 1, **mHTT**- Mutant huntingtin, **NMDAR**- N-methyl-D-aspartate receptor. **PPAR-γ**- Peroxisome proliferator-activated receptor gamma, **S1R**- Sigma 1 Receptor, **V1AR**- Vasopressin receptor 1a, **VMAT2**- Vesicular Monoamine Transporter 2.

Table 1. Clinical trials previously reviewed by the Huntington's Disease Clinical Trials Update.

	Trial Name	Intervention	Edition
NCT02519036	IONIS-HTTRx	IONIS-HTT$_{Rx}$	September 2017[1]
NCT02215616	LEGATO-HD	Laquinimod	
NCT02197130	Amaryllis	PF-02545920	
NCT02006472	PRIDE-HD	Pridopidine	
NCT03225833	PRECISION-HD1	WVE-120101	February 2018[2]
NCT03225846	PRECISION-HD2	WVE-120102	
NCT01795859	FIRST-HD	Deutetrabenazine	
NCT02481674	SIGNAL	VX15/2503	August 2018[3]
NCT00712426	CREST-E	Creatine	
NCT03761849	GENERATION-HD1	RG6042[4]	January 2019[4]
NCT02344602	PACE-HD	Physical activity	
NCT02535884	HD-DBS	Deep brain stimulation	June 2019[5]
NCT02453061	TRIHEP3	Triheptanoin	
NCT04120493	AMT-130	AAV5-miHTT	April 2020[6]
NCT04102579	KINECT-HD	Valbenazine	
NCT05111249	VIBRANT-HD	Branaplam	April 2022[7]
NCT04514367	ANX005	ANX-005	
NCT04514367	SHIELD HD	Observational study	
NCT03761849	GENERATION-HD1	Tominersen[7]	
NCT05032196	SELECT-HD	WVE-003	
NCT03225833	PRECISION-HD1	WVE-120101	
NCT03225846	PRECISION-HD2	WVE-120102	
NCT02481674	SIGNAL	Pepinemab[8]	November 2022[8]
NCT05358717	PIVOT HD	PTC518	
NCT05686551	GENERATION HD2	Tominersen[9]	August 2023[9]
NCT05541627	AB-1001	AAVrh10.CAG.hCYP46A1[10]	
NCT05822908	VO659-CT01	VO659	March 2024[11]
NCT05111249	VIBRANT-HD	Branaplam	
NCT06254482	PIVOT HD	PTC518 (extension study)	September 2024[12]
* NCT06585449	ALN-HTT02	ALN-HTT02	March 2025
* NCT05107128	DIMENSION	SAGE-718	
* NCT05655520	PURVIEW		

ALN-HTT02, single-dose intrathecal administration, RNAi therapy – Phase 1b, FIH study for safety, tolerability, PK/PD SAD
DB-RCT aims to recruit n=54 study participants with HD-ISS stage 2 or early stage 3 HD.

Kumar et al., 2023; Van De Roovaart et al., 2023; Estava-Fraga et al., 2024; Sampaio et al., 2024; Farag et al., 2025,

Other hot clinical trials items

The Digital Frontier in Huntington's Disease: Opportunities for Clinical Trials

Lori Quinn, PT, EdD, FAPTA,[1*] Matthew W. Roché, PhD,[2] Jonas Dorn, PhD,[3] and Jamie L. Adams, MD[4]

Motor function	Finger tapping, gait/stride length, trunk sway, other
Physical activity and sleep	Actigraphy, sleep
Cognition	App-based programs (SDMT)
Speech	Acoustic and linguistic extractions

Time to Functional Loss as an Endpoint in Huntington's Disease Trials: Enrichment and Sample Size

James A. Mills, MS,[1*] Jeffrey D. Long, PhD,[1,2] Jatin G. Vaidya, PhD,[1] Emily C. Gantman, PhD,[3] Swati Sathe, MD,[3] Sarah J. Tabrizi, MD, PhD,[4] and Cristina Sampaio, MD[3]

Modeling Disease Progression and Placebo Response in Huntington Disease

Insights From Enroll-HD and GENERATION HD1 Cohorts

Marcelo Boareto,[1] Yumi Yamamoto,[1] Jeffrey D. Long,[2,3] Cristina Sampaio,[4,5] Peter McColgan,[6] Cheikh Diack,[1,*] and Patricia Sanwald Ducray[1,*]

Neurology® 2023;104:e213646. doi:10.1212/WNL.0000000000213646

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Total functioning capacity scale in Huntington's disease: natural course over time

K. F. van der Zwaan[1] · S. Feleus[1,2] · O. M. Dekkers[2] · R. A. C. Roos[1] · S. T. de Bot[1]

Mills et al., 2024; Quinn et al., 2025; Boareto et al., 2025; Van Der Zwaan et al., 2025

