REVIEW

Systematic Review of the Huntington's Disease Drug Development Pipeline, 2014 to 2025

Pavlina Konstantinova, PhD, MBA,[1] Jenny Townhill, PhD,[1,2] Juliana Bronzova, MD, DSc,[1] Viktoria Andreeva, PhD,[3] Swati Sathe, MD,[4] and Cristina Sampaio, MD, PhD[4*]

ABSTRACT: Background: In the past decade, significant advances have improved our understanding of the mechanisms underlying HD pathobiology leading to several putative therapeutic targets for HD.
Objective: The aim was to describe the Huntington's disease (HD) drug development clinical pipeline.
Methods: We analyzed all HD clinical trials described in clinicaltrials.gov and the WHO International Clinical Trials Registry from January 1, 2014, to November 13, 2025. Studies were classified as interventional (pharmacological and nonpharmacological) or observational (natural history, biomarker, and other). Interventional trials were further categorized according to phase of development and type of intervention. Proposed mechanisms of action were classified according to adapted Common Alzheimer's and Related Dementias Research Ontology definitions, with huntingtin lowering assigned as a separate category.
Results: A total of 165 registered clinical studies for Huntington's disease (HD) were identified between 2014 and the index date, requiring 7501 participants. These included 54 observational studies and 111 interventional trials. Of the 69 pharmacological trials, 54.9% have been completed, 10.8% have been terminated, and 39.2% remain active. Over the past 11 years, 50 different pharmacological agents have been tested in 69 trials, with 21 agents currently being evaluated. Disease-modifying therapies now account for 90.5% of phase 1 trials, 61.8% of phase 2 trials, and 55.6% of phase 3 trials in the pipeline.
Conclusions: Over the past decade, the HD clinical trial landscape has expanded and shifted toward disease-modifying strategies, with significant changes in trial design and a shift in the target population to an earlier stage of disease.

Key Words: disease modifying; Huntington's disease; pipeline; symptomatic

Currently, there is no licensed disease-modifying therapy (DMT) for Huntington's disease (HD), and the only approved drugs are specifically indicated for chorea. HD drug development has long faced significant challenges, with numerous phase 2 and 3 trials failing to demonstrate efficacy or encountering safety concerns. Active research is now mainly focusing on therapies targeting disease-specific mechanisms at various stages of drug development.[1]

For other diseases, such as Alzheimer's,[2] careful descriptions of the therapeutic landscape are published regularly. In HD, although regular clinical trial updates are published,[3,4] a systematic review of the history and evolution of the HD drug development pipeline over

[1]European Huntington's Disease Network, University Hospital of Ulm, Ulm, Germany; [2]School of BioSciences, Cardiff University, Cardiff, United Kingdom; [3]Rancho BioSciences, San Diego, California, USA; [4]CHDI Management, Inc., Princeton, New Jersey, USA

***Correspondence to:** Dr. Cristina Sampaio, CHDI Management, Inc., 115 Village Boulevard, Suite 200, Princeton, NJ 08540, USA; E-mail: cristina.sampaio@chdifoundation.org

Pavlina Konstantinova and Jenny Townhill have contributed equally to this study.

Relevant conflicts of interest/financial disclosures: P.K. and J.B. are employed by the European Huntington's Disease Network. J.T. is employed by Cardiff University and the European Huntington's Disease Network. V.A. is employed by Rancho BioSciences. S.S. and C.S. are employed by CHDI Management, Inc., the company that manages the scientific activities of CHDI Foundation, Inc.
Funding agency: This study was funded by CHDI Foundation, Inc.

Received: 15 July 2025; **Revised:** 7 February 2026; **Accepted:** 8 May 2026

Published online in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mds.70361

the past decade is not available. Here we have assessed the HD clinical research landscape over the last decade, including therapeutic purpose, mechanism of action, required number of participants, duration, global distribution, and funding.

Patients and Methods

Clinical Trial Metadata Extraction

Full methodologic details are provided in Supplement S1. Briefly, we searched the clinicaltrials.gov database and the International Clinical Trials Registry Platform[5] using the keyword "Huntington(s) disease." Duplicate entries were consolidated so that each trial appeared only once. Trials were reported according to their published development phase.

Trial-reported outcomes were identified from scientific publications. PubMed was queried using a custom crawler tool (Rancho BioSciences). Searches were conducted using clinical trial number, trial acronyms, and drug names. Search results were manually reviewed, and relevant publications were selected. A custom *Python* script was used to systematically extract trial outcomes from publications. Trial design elements and outcome measures were comprehensively extracted and structured in JSON format. All extracted results underwent manual verification.

Clinical Trial Metadata Analysis

The index date for this review is November 13, 2025. It includes all HD-specific trials classified as completed, terminated, active—recruiting, active—not recruiting, enrolling by invitation (including open-label extensions of prior double-blind trials), and not yet recruiting (these are included in the count of active trials in this review). Trials that began before January 1, 2014, were not registered on the index date, or primarily enrolled healthy volunteers or participants with other diseases were excluded. Studies that had the main population as HD but also included individuals with related conditions (eg, spinocerebellar ataxia or Parkinson's disease [PD]) were retained (Supplement S2). Trials marked as withdrawn were excluded.

HD clinical studies were divided into interventional (efficacy evaluation of biomarkers and therapeutics [pharmacological and nonpharmacological]) and observational studies (categorized as natural history, biomarker, and other), and the number of studies per year was calculated from the registered trial initiation date. Interventional pharmacological trials were categorized into those with potential DMTs or symptomatic treatments, depending on the declared therapeutic purpose. We derived the target and mechanism of the pharmacological agent based on the specific target or pathway and biochemical interactions according to an adaptation of the Common Alzheimer's and Related Dementias Research Ontology (CADRO) database, which is a three-tiered classification system to organize and compare basic, translational, and clinical research projects across multiple funding organizations using common terminology. Categories include neurotransmitter receptors, inflammation, oxidative stress, metabolism and bioenergetics, cell death, growth factors and hormones, synaptic plasticity/neuroprotection, epigenetic regulators, cell replacement therapies, and "other." Because an ontology specific to HD does not exist, we used CADRO categories when applicable and assigned huntingtin (HTT) lowering as a separate category.

Therapeutic agents were categorized as nucleic acid therapies (eg, antisense oligonucleotides [ASOs], small interfering RNAs [siRNAs]), antibodies, advanced therapies (cell and gene therapy), small molecules, and supplements. We classified repurposing trials as the utilization of a known compound, licensed by the U.S. Food and Drug Administration (FDA) or the European Medicines Agency (EMA), in a novel indication, suggesting a new mechanism of action that predicts innovative therapeutic options.[6] Trials of nonpharmacological interventions included behavioral interventions (divided into cognitive and physical), procedure/devices, and diet and dietary supplements. Biomarkers were defined as a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to an intervention.[7]

Results

Overall, 165 registered clinical studies for HD were identified between 2014 and the index date, comprising 54 observational studies (32.1%) and 111 interventional trials (67.9%). A PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) diagram is shown in Supplement S3, Figure e1, and a searchable summary of trials is provided in Supplement S2, Tables S1-S4. Most of the interventional trials evaluated the therapeutic safety and efficacy of pharmacological ($n = 69$) or nonpharmacological treatments ($n = 33$), and nine evaluated biomarker utility. A breakdown of the studies by study type is shown in Figure 1A. Figure 1B shows that about half (56/102, 54.9%) of the therapeutic trials in the 11-year pipeline have been completed, 11 (10.8%) have been terminated, and 30 (39.2%) are active.

Interventional Trials

The status of the 33 diverse nonpharmacological trials categorized into behavioral-cognitive, behavioral-physical, diet, and device interventions is provided in

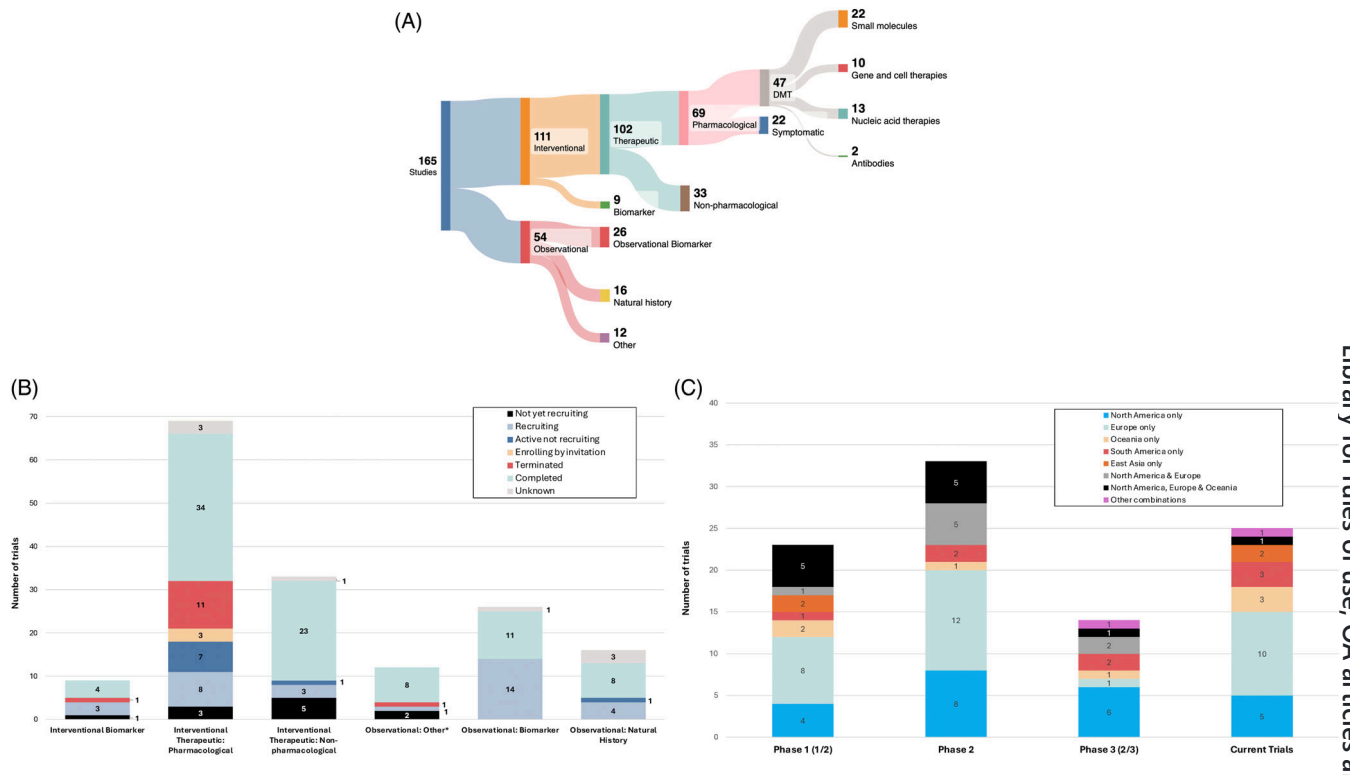

FIG. 1. Clinical studies in HD 2014 to 2024 by **(A)** study type, **(B)** current status, and **(C)** geographic distribution. *"Observational: Other" trials include observational studies with a primary objective of cognition, novel assessments, pain, suicide, out-of-pocket costs, caregiver support, or real-world evidence. [Color figure can be viewed at wileyonlinelibrary.com]

Supplement S3, Figure e2, and the rest of this review focuses on pharmacological interventions.

Over 11 years, 69 pharmacological trials were identified: 21 phase 1 (including phase 1/2), 34 phase 2, 13 phase 3 (including phase 2/3), and 1 phase 4 trial (Supplement S3, Table e1). These trials assessed 50 pharmacological agents (21 in active trials), with several agents (eg, AMT-130, NestaCell, pridopidine, PTC518, SAGE-718, tominersen) appearing in multiple phases and different trials. Table 1 summarizes all DMT trials (n = 32 agents in 47 trials), and Table 2 presents symptomatic therapies (n = 18 agents in 47 trials). Most phase 1 trials (90.5%, n = 19) evaluated DMTs, including 7 nucleic acid therapies, 5 advanced therapies, and 4 small molecules. The share of DMT trials decreased in phase 2 (61.8%, n = 21) and phase 3 (55.6%, n = 7), which included combinations of nucleic acid therapies, cell therapies, antibodies, and small molecules or supplements. Symptomatic therapies were rare in phase 1 (two trials, both small molecules) but more common in phase 2 (38.2%, n = 13) and phase 3 (46.2%, n = 6), primarily targeting neurotransmitter receptors. Note that some trials tested multiple agents simultaneously, and some agents progressed through several phases.

CADRO classification of the 50 pharmacological agents is shown in Figure 2A and Supplement S3, Table e2. Phase 1 (1/2) trials currently address four adapted CADRO biological process categories alongside strategies for lowering HTT. In phase 2, agents target eight adapted CADRO categories, with a continued emphasis on HTT reduction. Phase 3 (2/3) trials primarily focus on five agents acting on neurotransmitter receptors, whereas others target metabolism and bioenergetics, HTT lowering, or cell replacement therapy. Particularly, two phase 3 trials are long-term open-label extension studies of valbenazine, which is already approved for marketing in the United States.

Pipeline trends reveal a shift from symptomatic treatments to DMTs. Figure 2B shows the cumulative number of active trials per year. Between 2014 and 2015, small molecules for symptomatic treatment comprised half of the new compounds entering the pipeline (n = 3), increasing to 83.3% (n = 5) in 2017 and 80% (n = 4) in 2019. By contrast, DMTs accounted for 80% (n = 4) of new agents in 2021 and all new agents introduced between 2022 and 2025.

Over the past 11 years, pharmacological trials have enrolled 7501 participants. Of these, 1968 participants are required for the 21 currently active interventional therapeutic pharmacological trials, including 1727 for DMT trials currently recruiting and 241 for active symptomatic trials (Table 3). Phase 2 trials enrolled the largest number of participants at 4201, followed by phase 3 (2/3) trials with 2480 and phase 1 (1/2) trials with 787 participants. Mean enrollment per trial type

TABLE 1 Overview of all DMT trials

DMT trials	Phase 1	Phase 1/2	Phase 2	Phase 2/3	Phase 3	Grand total
Antibody	–	–	2 (100)	–	–	**2**
ANX005	–	–	1 (100)	–	–	1
VX15/2503	–	–	1 (100)	–	–	1
Cell therapy	2 (33.3)	–	2 (33.3)	1 (16.7)	1 (16.7)	**6**
Fetal striatal cells	1 (50.0)	–	1 (50.0)	–	–	2
NestaCell	1 (25)	–	1 (25.0)	1 (25.0)	1 (25.0)	4
Gene therapy		4 (100)	–	–	–	**4**
AB-1001	–	1 (100)	–	–	–	1
AMT-130	–	2 (100)	–	–	–	2
SPK-10001	–	1 (100)	–	–	–	1
Nucleic acid therapy	2 (15.4)	7 (53.8)	2 (15.4)	–	2 (15.4)	**13**
ALN-HTT02	1 (100)	–	–	–	–	1
ER2001	1 (100)	–	–	–	–	1
Tominersen (ISIS 44313)	–	1 (100)	–	–	–	1
Tominersen (RO723429)	–	–	1 (33.3)	–	2 (66.7)	3
Tominersen	–	–	1 (100)	–	–	1
VO659	–	1 (100)	–	–	–	1
WVE-001	–	2 (100)	–	–	–	2
WVE-002	–	2 (100)	–	–	–	2
WVE-003	–	1 (100)	–	–	–	1
Small molecule	3 (13.6)	1 (4.5)	15 (68.2)	1 (4.5)	2 (9.1)	**22**
BN82451B	–	–	1 (100)	–	–	1
Branaplam	–	–	1 (100)	–	–	1
Felodipine	–	–	1 (100)	–	–	1
Laquinimod	–	–	1 (100)	–	–	1
MBF-015	–	–	1 (100)	–	–	1
Metformin	–	–	–	–	1 (100)	1
MP-101	1 (100)	–	–	–	–	1
N-Acetyl cysteine[a]	–	–	1 (100)	–	–	1
Neflamapimod	–	–	1 (100)	–	–	1
Nicotinamide riboside[a]	–	–	1 (100)	–	–	1
Nilotinib	1 (100)	–	–	–	–	1
Pridopidine	–	–	2 (66.7)	–	1 (33.3)	3
PTC518 (votoplam)	–	–	2 (100)	–	–	2
Resveratrol[a]	–	–	1 (100)	–	–	1
SBT-020	–	1 (100)	–	–	–	1
SKY-0515	1 (50)	–	–	1 (50.0)	–	2
Thiamine with biotine[a]	–	–	1 (100)	–	–	1
Triheptanoin	–	–	1 (100)	–	–	1
Grand total	**7**	**12**	**21**	**2**	**5**	**47**

Note: Data are number of trials (% in each category). Bold values indicate the total number of trials per category.
Abbreviation: DMT, disease-modifying therapy.

TABLE 2 Overview of all symptomatic trials

Symptomatic trials	Phase 1	Phase 2	Phase 2/3	Phase 3	Phase 4	Grand total
Small molecule	2 (9.1)	13 (59.1)	1 (4.5)	5 (22.7)	1 (4.5)	**22**
Deutetrabenazine	–	–	1 (50)	–	1 (50)	2
Nuedexta^	–	–	–	1 (100)	–	1
Fenofibrate	–	1 (100)	–	–	–	1
Haloperidol[a]	1 (100)	–	–	–	–	1
Lactobacillus[b,c]	–	1 (100)	–	–	–	1
Melatonin[b]	–	1 (100)	–	–	–	1
OMS643762	–	1 (100)	–	–	–	1
OSU6162	–	1 (100)	–	–	–	1
PF-02545920	–	2 (100)	–	–	–	2
Risperidone	–	1 (100)	–	–	–	1
SAGE-718	1 (25.0)	2 (50)	–	1 (25.0)	–	4
SOM3355	–	2 (100)	–	–	–	2
SRX246	–	1 (100)	–	–	–	1
Valbenazine	–	–	–	3 (100)	–	3
Grand total	**2 (9.1)**	**13 (59.1)**	**1 (4.5)**	**5 (22.7)**	**1 (4.5)**	**22**

Note: Bold values indicate the total number of trials per category.
^Dextromethorphan and quinidine.
[a]Haloperidol, risperidone, Zoloft, idebenone, and deutetrabenazine.
[b]Supplements.
[c]*Lactobacillus rhamnosus*, *Saccharomyces cerevisiae*, *Bifidobacterium animalis* ssp. *lactis*.

also differed by therapy class and phase. In phase 1 (1/2), averages were 16.8 participants for DMT advanced therapies, 48.8 for nucleic acid therapies, 37 for DMT small molecules, and 33 for symptomatic therapies. In phase 2, these increased to 37 for DMT advanced therapies, 147.7 for nucleic acid therapies, 170.5 for antibody therapies, 154.7 for DMT small molecules, and 113.7 for symptomatic therapies. Phase 3 trials were largest, averaging 308 participants for DMT therapies and 89 for symptomatic therapies. Using the 1979 Shoulson and Fahn staging system,[8] 93.8% (n = 61) of trials were conducted in individuals with HD after clinical motor diagnosis, with only 4 (6.2%) trials explicitly including participants before motor diagnosis.

The average phase 1 trial duration was 381.7 weeks for advanced (cell and gene) therapies and 136.4 weeks for nucleic acid therapies and small molecule therapies. Average trial durations were 147.2 weeks for phase 2 trials and 150.8 weeks for phase 3 trials, although the higher proportion of symptomatic trials should be noted.

Biomarkers

Of the nine interventional biomarker trials, five evaluated the sensitivity of the newly developed or existing positron emission tomography radioligands and magnetic resonance imaging, one looked at the D2/D3 and S1R receptor occupancy of pridopidine, and one was a pharmacokinetic (PK)/pharmacodynamic (PD) study of tominersen in plasma and cerebrospinal fluid. Overall, 20 (28.9%) of the pharmacological trials testing 15 agents had biomarkers as outcome measures: 12 (57.1%) in phase 1 (1/2), 6 (17.6%) in phase 2, and 2 (15.4%) in phase 3 (2/3). The most commonly used biomarkers were levels of HTT protein, neurofilament light chain (NfL), and caudate volume. Note that not all outcomes are listed in clinicaltrials.gov.

Current Drug Pipeline

There are currently 21 registered ongoing and planned trials testing 17 compounds, with 15 initiated in the past 2 years (Fig. 2; Supplement S3, Fig. e3). The earliest active trial began in 2019 for AMT-130 (NCT04120493). Note that one trial (NCT04071639) that tested a combination of three repurposed and two agents approved for HD is not summarized in Figure 2 as there are no reports on its progress. Considered together, current pharmacological trials require 1968 participants, the majority (n = 1145) in phase 2 trials.

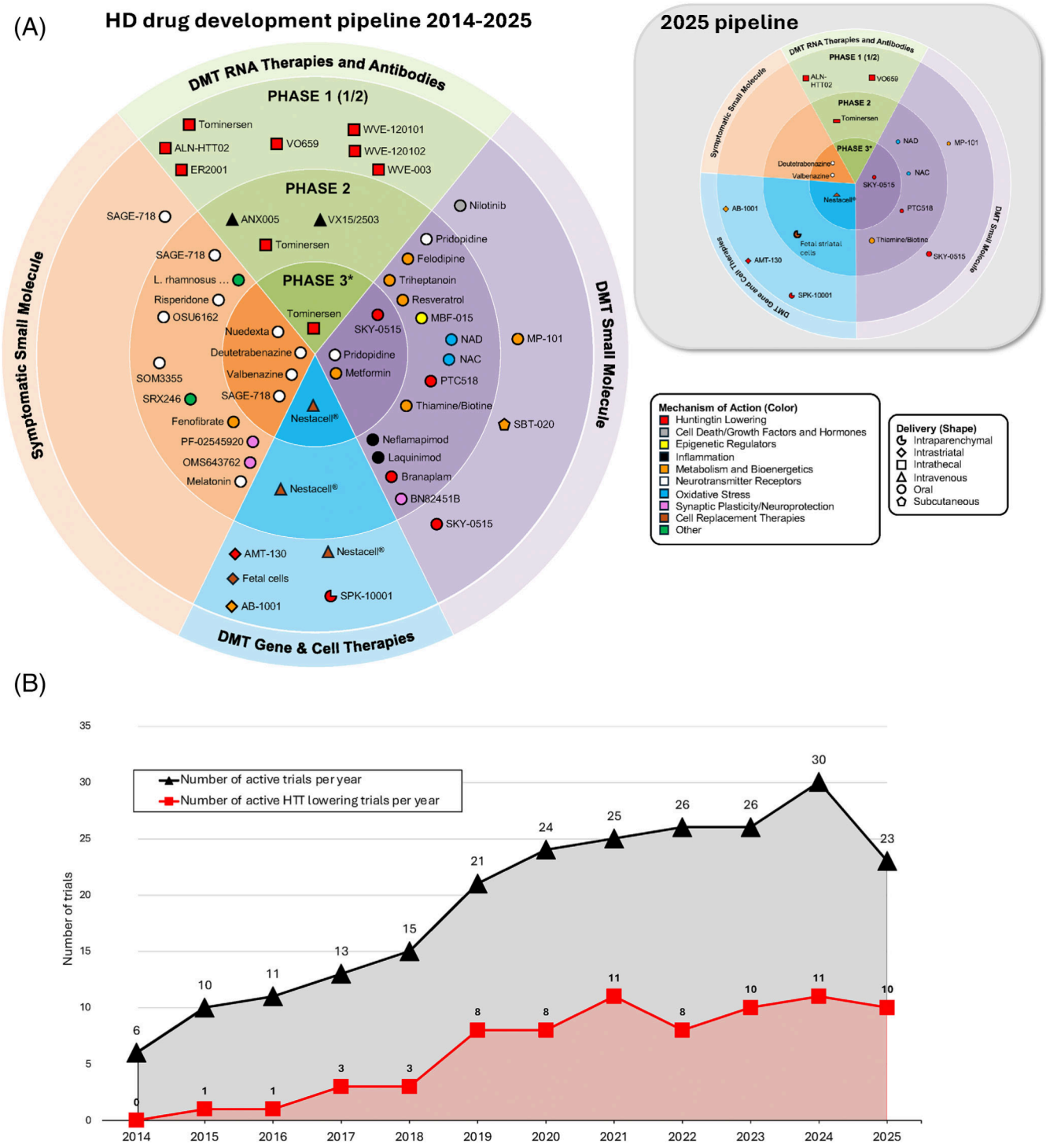

FIG. 2. HD (Huntington's disease) drug development pipeline **(A)** by phase* and mechanism of action and **(B)** cumulative number of active studies per year#. *Some agents appear multiple times according to development phases. Number of current trials for 2025 are shown in Supplement S3, Figure e3. Agents categorized as epigenetic regulators, oxidative stress and cell death/growth factors, and hormones (n = 1 each) are grouped under "other" targets. #Note that the total number of active trials (in black) includes the trials for HTT-lowering agents (in red). [Color figure can be viewed at wileyonlinelibrary.com]

Global Trial Funding and Distribution

Overall, 50 (72.5%) of the 69 pharmacological clinical trials were industry funded, including 9 (69.2%) phase 3 (2/3) trials, 22 (64.7%) phase 2 trials, and 17 (81.0%) phase 1(1/2) trials. The majority of the trials were conducted in North America and/or Europe (86.1%). As shown in Figure 1C, most phase 1 trials were conducted in Europe (38%) and North America (19%), phase 2 trials were concentrated in Europe (33%) and North America (24%), and phase 3 trials

TABLE 3 Target enrollment for pharmacological trials by phase and purpose of treatment (DMT/symptomatic therapy)

	DMT enrollment		Symptomatic enrollment				Active	
	All trials	Active trials	All trials	Active trials	Total enrollment all	Percentage enrollment all	Total enrollment active	Percentage enrollment active
Phase 1	221 (7)	168 (3)	66 (2)	–	287 (9)	3.8	168 (3)	8.5
Phase 1/2	503 (12)	174 (5)	–	–	503 (12)	6.7	174 (5)	8.8
Phase 2	2851 (21)	1145 (7)	1350 (13)	–	4201 (34)	56.0	1145 (7)	58.2
Phase 2/3	155 (2)	120 (1)	30 (1)	30 (1)	185 (3)	2.5	150 (2)	7.6
Phase 3	1814 (5)	120 (1)	461 (5)	161 (2)	2275 (1)	30.3	281 (3)	14.3
Phase 4	–	–	50 (1)	50 (1)	50 (1)	0.7	50 (1)	2.5
Grand total	**5544 (47)**	**1727 (17)**	**1957 (22)**	**241 (4)**	**7501 (69)**	**100.0**	**1968 (21)**	100

Note: N = 69 all trials, N = 21 active trials. Bold values indicate the total number of trials per category.
Abbreviation: DMT, disease-modifying therapy.

were dominated by North America (46%). Current trials are primarily in Europe (48%) and North America (24%), with smaller proportions in Oceania, South America, and East Asia.

Publication of Trial Results

Twenty-two (66.7%) of the 33 completed pharmacological trials had published results in the clinical trial registry databases (Supplement S2), and 19 (7.5%) trials had published results in peer-reviewed journals (phase 1, n = 4[9-12]; phase 2, n = 10[10-23]; phase 3, n = 2[24-27]). Twelve trials measured components of the Unified Huntington's Disease Rating Scale (UHDRS) as a primary end point, and five trials had safety as a primary end point. Four trials reported biomarker measurements as secondary or exploratory end points of pharmacological efficacy. The median gap between trial completion date and trial publication date was 3.5 years. There were 49 public reports (press releases, publications, conference abstracts, and presentations) announcing results from 33 pharmacological clinical trials testing 23 agents between 2014 and the index date (Supplement S2).

Discussion

Our systematic review shows sustained interest in HD drug development, with the overall number of studies and annual trial initiations remaining relatively constant. However, the nature of interventions has shifted, with the past 5 years characterized by a significant increase in industry-funded DMT trials, particularly at phase 2. Geographically, most studies are concentrated in Europe and North America.

Our analysis shows that more interventional trials and agents have been evaluated in the past decade compared to the previous period.[28] The evolution of the drug development pipeline indicates that mostly agents aimed at symptomatic treatment entered the pipeline between 2014 and 2019, whereas from 2021 to 2024 nearly all new agents were DMTs. The share of DMT agents has grown from 43.4% in the 15-year period through 2017[28] to 64.3% (27 agents). It is noteworthy that pridopidine was originally developed as a symptomatic treatment, but the classification is now DMT, as the proposed mechanism of action has been updated during development (from a dopaminergic stabilizer to a sigma-1 receptor agonist). It is the most extensively tested drug in HD, in terms of patient-years exposure,[25] despite failing to reach significance on primary outcomes.

Currently, only 8.2% of the pipeline targets symptomatic treatment. This number is comparable to Alzheimer's disease, where 78% of the agents currently under investigation are DMTs.[2] In HD, four different advanced therapy agents are being evaluated in eight registered trials. The registered trial involving fetal striatal cells is a follow-up study of participants from a completed phase 2 trial.[29] The AB-1001 trial remains recorded as active, although the program has been discontinued. The status of the phase 2/3 NestaCell extension trial is currently unknown, and the phase 3 trial has not yet commenced.

A recent press release reported 3-year phase 1/2 data of AMT-130 in 12 individuals with early HD (HD Integrated Staging System [HD-ISS] stages 2 and 3), citing a 75% reduction in composite UHDRS decline versus propensity-matched Enroll-HD controls and a favorable NfL profile.[30] Although previously considered a potentially acceptable basis for filing, more recently the FDA determined that these data were insufficient, contributing to growing uncertainty among sponsors about evidentiary expectations in the USA.

Overall, the 50 therapeutic agents for HD addressed 8 adapted CADRO categories and HTT lowering. The most commonly tested compounds target neurotransmitter receptors (12 agents) and different HTT-lowering

DMT molecules (12 compounds). The high number of HTT-targeting therapies in the clinical pipeline reflects more than 20 years of research on the structure, function, and pathological effects of the HTT mRNA and protein in multiple model systems.[31,32] Including a new trial initiated after our index date (NCT07246941), the current pipeline includes 11 trials evaluating 8 HTT-lowering agents. Of these, only three (VO659, WVE-003, and RG6496) are allele-selective/preferential oligonucleotides, whereas the remaining agents target both wild-type and mutant HTT. Three agents in the pipeline (AMT-130, ALN-HTT02, and VO659) address HTT exon 1 toxicity, and SKY-0515 also lowers PMS1. The HD field is uniquely rich in research tools and assays, small and large animal models, patient data, and observational clinical platforms that continuously support the development of clinical trials. However, as evidenced by the diversity of clinical and biomarker outcomes used as primary and secondary outcomes in current trials, more work is needed on how to demonstrate meaningful effects. This is especially important for HD-ISS stage 2, which is currently the primary target population for DMT, as is a stage where clinical symptoms and signs can be subtle but still measurable. Ongoing efforts to improve outcome measures and biomarkers will enhance the trial environment in HD.

Overall, only 12 (24.5%) agents (3 advanced therapies, 6 nucleic acid therapies, and 3 small molecules) from the 50 pipeline agents were specifically designed for HD. That only two agents (MBF-015 and PTC518) have been tested in both phase 1 healthy-volunteer trials can be explained by the prior conduct of phase 1 studies for development in other conditions and by the fact that many HD-specific DMTs are not tested on healthy volunteers. Four agents (8.2%, tominersen, NestaCell, pridopidine, and SAGE-718) progressed from phase 2 to phase 3, whereas three (6.1%, deutetrabenazine, metformin, and valbenazine) were tested in phase 3 trials. Tominersen was evaluated in a phase 1/2 trial, followed by a phase 3 trial that was discontinued due to safety concerns. A phase 2 trial was subsequently initiated in earlier-stage patients at a lower dose. The phase 3 trial for NestaCell has yet to start, and the SAGE-718 program for HD has been discontinued. Within the current pipeline, advanced therapies have started to follow a hybrid approach, where phase 1/2 trials are intended to provide a sufficient level of confirmatory evidence for approval. However, the regulatory path forward for this approach is currently being established.

Of the 30 evaluated agents with completed trials, only deutetrabenazine (USA, Israel, and Australia) and valbenazine (USA) have received approval in the past 10 years. Although published within the current time frame, the pivotal deutetrabenazine trial[33] was not included in this current review as it started in 2013. As reported previously, compared with other neurodegenerative diseases, HD clinical trial success rates are higher from phases 1 to 2 but generally lower from phases 2 to 3 and from phase 3 to regulatory approval.[28] For the studies included in this review time frame, the success rate for therapeutic development in HD is about 3%, compared with 19% for Alzheimer's disease,[34] 15% for PD,[35] and 4% to 12% for amyotrophic lateral sclerosis.[36] The likelihood of success for a single compound in HD is also considerably lower than that in other rare diseases. However, arguably, the most innovative drugs under development for HD are still undergoing clinical testing. The older group of drugs tested had weaker mechanistic rationales, contributing to a lower likelihood of success from the outset. In 2014, the success rate of orphan drugs, in general, was 86.8% from phases 1 to 2, 70.0% from phases 2 to 3, and 66.9% from phase 3 to approval.[37]

The majority of observational studies were biomarker studies testing neuroimaging biomarkers. Particularly, our reference period does not include several prospective observational studies that have been completed (eg, TRACK-HD, TrackOn-HD, PREDICT-HD, and IMAGE-HD) or those that are ongoing, including Enroll-HD.[38] Enroll-HD is the world's largest study in HD and an integrated clinical research platform that has recruited more than 31,000 participants.[1,38] As the primary ongoing observational study it provides contemporaneous natural history data that have recently been used as an external comparator in controlled clinical trials.[30,39] In addition, these studies have provided high-profile datasets that have been used to build staging models, identify genetic modifiers, investigate mechanisms of progression, and guide clinical trial design.[40-43]

Historically, most clinical trials aimed to enroll participants with a clinical motor diagnosis of HD, and accordingly, we found that the population included in the clinical trial pipeline is usually relatively advanced. However, due to a previous lack of systematic disease staging criteria, we observed that trials used a multitude of different inclusion criteria. The 2022 publication, and more widespread adoption, of the HD-ISS[42] as a new framework that describes the whole continuum of HD from birth to death should help better define the target population in clinical trials.[43] However, its use still requires supplementary selection criteria, drawing on established measures such as the CAG-age product (CAP), normalized prognostic index (PIN), UHDRS total motor score (TMS), and total functional capacity (TFC) to define the most appropriate participant subgroups. It is also pertinent to note that, although HD is a rare disease, no studies were discontinued early due to poor recruitment, which may, at least in part, be explained by the significant contribution of the Enroll-HD research platform[38] in supporting the clinical

development landscape. However, the growing trend toward including participants before clinical motor diagnosis highlights the need for the Enroll-HD study to put further measures into place to facilitate the recruitment of earlier-stage populations.

The duration of trials in each phase provides insight into the time required for drug development programs for HD. On average, current HD drugs require 9.8 years (from registered start date to registered completion date) to complete trials in phases 1–3. Importantly, the trial duration of phase 1 (1/2) trials with advanced therapies was almost thrice longer than that of nucleic acid therapies, antibodies, or small molecules (85 vs. 30.5 months, respectively), and this accounts for the increased trial duration from prior pipeline overviews (the mean length of phase 1, phase 2, and phase 3 trials was previously reported to be 103, 279, and 456 days, respectively[28]). Of note, only 26.2% of the pharmacological trials reported biomarkers as outcomes of pharmacological efficacy. This number is lower than that for other neurodegenerative diseases, where 54% of the trials performed between 2010 and 2020 used target engagement biomarkers.[44] Due to the current focus on DMT, the ongoing development of novel assays and technologies for NfL and HTT detection and neuroimaging is critical to addressing this urgent issue.

Overall, the data in this work encompass a dynamic period in which clinical drug development has shifted from repurposed drugs or supplements to a proliferation of targeted therapies, driven by small biotech firms and the pharmaceutical industry. This scientific evolution has also led to significant changes in funding. We observed a limited footprint of nonindustry funding sources in HD, with most (74.0%) being funded, at least in part, by commercial entities. This already represents an increase compared to the previously reported 60% industry-funded trials during 1999 to 2017[28] and is now comparable to Alzheimer's disease, where 78% of clinical trials are industry funded.[34] We observed a paucity of trials in South America, which would otherwise be a very relevant region due to the comparatively higher prevalence of HD in countries such as Venezuela, Colombia, Peru, and parts of Brazil.[45] Although there are well-established HD research centers in these countries, trial involvement has been relatively limited due to factors such as access to genetic testing and limited availability of movement disorders specialists[45]; regulatory factors also impact. Only 51.5% of the completed pharmacological trials have been reported in peer-reviewed publications, which is a relatively low rate but comparable to what has been reported previously in neurology trials[46] and trials for rare diseases.[47] Unfortunately, this aligns with the trend of low publication rates for clinical trials in general,[48] which has been improving in the United Kingdom after political pressure and transparency initiatives,[49] but remains low in other geographies. The timely publication of trial results is crucial for building on learnings, avoiding repetition of mistakes, and facilitating innovative techniques like Bayesian analysis which depend on prior informative data.

An unavoidable limitation of our analysis is time. Just 1 week after our defined index date, a first-in-human trial of a novel HTT-lowering agent commenced (NCT07246941). In addition, there are publicly disclosed trials in planning but not yet registered, including HTT-lowering studies: two phase 1 trials of novel agents (ATL-101, SRP-1005), two phase 2/3 trials (SKY-0151, WVE-003), and a phase 3 trial of votoplam. Pridopidine is expected to undergo another phase 3 trial after a withdrawn EMA marketing application, and SOM3355 is anticipated to advance to a potentially registrational phase 3 trial. Other known DMT agents in preclinical and clinical development involve mechanisms beyond adapted CADRO classifications, particularly targeting somatic instability and prime editing approaches. Another key limitation is the reliance on public trial registries. Although registered study sponsors are legally required to provide data and regular updates, this has not been well enforced until recently, and the frequency of updates and the extent of information reported are largely at a sponsor's discretion. Similarly, there is currently no mechanism to ensure timely updates or to report on discontinued programs. Therefore, the raw data on which this analysis is based are known to be somewhat deficient and favoring, in terms of quantity and detail, industry-funded programs.

Author Roles: (1) Research project: A. Conception, B. Organization, C. Execution; (2) Statistical analysis: A. Design, B. Execution, C. Review and critique; (3) Manuscript preparation: A. Writing of the first draft, B. Review and critique.
P.K.: 1A, 1B, 1C, 2A, 2B, 3A, 3B
J.T.: 1A, 1B, 1C, 2B, 2C, 3A, 3B
J.B.: 1A, 1C, 2B, 2C, 3B
V.A.: 1C, 2C, 3B
S.S.: 2C, 3B
C.S.: 1A, 2C, 3B

Acknowledgments: We thank Jennifer Ware and Simon Noble (CHDI) for their assistance with the paper. Medical writing assistance was provided by Anita Chadha-Patel of ACP Clinical Communications (Hertfordshire, UK) and was supported by CHDI in accordance with Good Publication Practice guidelines.

Full financial disclosures of all authors for the previous 12 months: P.K. and J.B. are employed by the European Huntington's Disease Network. P.K. is CEO of PLaN Therapeutics, the Netherlands. J.T. is employed by Cardiff University and the European Huntington's Disease Network. V.A. is employed by Rancho BioSciences. S.S. and C.S. are employed by CHDI Management, Inc., the company that manages the scientific activities of CHDI Foundation, Inc.

Financial Disclosures and Conflicts of Interest: Author disclosures are available in the Supporting Information.

Data Availability Statement

All data supporting this work are available in this article and the supplementary tables.

References

1. Sampaio C. Huntington disease – update on ongoing therapeutic developments and a look toward the future. Parkinsonism Relat Disord 2024;122:106049.
2. Cummings JL, Zhou Y, Lee G, Zhong K, Fonseca J, Leisgang-Osse AM, Cheng F. Alzheimer's disease drug development pipeline: 2025. Alzheimers Dement (N Y) 2025;11(2):e70098.
3. Estevez-Fraga C, Tabrizi SJ, Wild EJ. Huntington's disease clinical trials corner. J Huntingtons Dis 2024;13(1):1–14.
4. van de Roovaart HJ, Nguyen N, Veenstra TD. Huntington's disease drug development: a phase 3 pipeline analysis. Pharmaceuticals 2023;16(11):1513. https://doi.org/10.3390/ph16111513
5. International Clinical Trials Registry Platform (ICTRP); https://www.who.int/tools/clinical-trials-registry-platform/the-ictrp-search-portal.
6. Langedijk J, Mantel-Teeuwisse AK, Slijkerman DS, Schutjens MH. Drug repositioning and repurposing: terminology and definitions in literature. Drug Discov Today 2015;20(8):1027–1034.
7. Frank R, Hargreaves R. Clinical biomarkers in drug discovery and development. Nat Rev Drug Discov 2003;2(7):566–580.
8. Shoulson I, Fahn S. Huntington disease: clinical care and evaluation. Neurology 1979;29(1):1–3.
9. Anderson KE, Stevenson M, Varghese R, et al. Alteration of autophagy and glial activity in nilotinib-treated Huntington's disease patients. Metabolites 2022;12(12):1225.
10. Hawellek DJ, Garces P, Meghdadi AH, et al. Changes in brain activity with tominersen in early-manifest Huntington's disease. Brain Commun 2022;4(3):fcac149.
11. Tabrizi SJ, Leavitt BR, Landwehrmeyer GB, et al. Targeting huntingtin expression in patients with Huntington's disease. N Engl J Med 2019;380(24):2307–2316.
12. Fernandes JMS, Pagani E, Wenceslau CV, Ynoue LH, Ferrara L, Kerkis I. Phase II trial of intravenous human dental pulp stem cell therapy for Huntington's disease: a randomized, double-blind, placebo-controlled study. Stem Cell Res Ther 2025;16(1):432.
13. Reilmann R, Anderson KE, Feigin A, et al. Safety and efficacy of laquinimod for Huntington's disease (LEGATO-HD): a multicentre, randomised, double-blind, placebo-controlled, phase 2 study. Lancet Neurol 2024;23(3):243–255.
14. Roussakis AA, Gennaro M, Gordon MF, et al. A PET-CT study on neuroinflammation in Huntington's disease patients participating in a randomized trial with laquinimod. Brain Commun 2023;5(2):fcad084.
15. Gamez J, Calopa M, Muñoz E, et al. A proof-of-concept study with SOM3355 (bevantolol hydrochloride) for reducing chorea in Huntington's disease. Br J Clin Pharmacol 2023;89(5):1656–1664.
16. Feigin A, Evans EE, Fisher TL, et al. Pepinemab antibody blockade of SEMA4D in early Huntington's disease: a randomized, placebo-controlled, phase 2 trial. Nat Med 2022;28(10):2183–2193.
17. Reilmann R, McGarry A, Grachev ID, et al. Safety and efficacy of pridopidine in patients with Huntington's disease (PRIDE-HD): a phase 2, randomised, placebo-controlled, multicentre, dose-ranging study. Lancet Neurol 2019;18(2):165–176.
18. Underwood BR, Green-Thompson ZW, Pugh PJ, et al. An open-label study to assess the feasibility and tolerability of rilmenidine for the treatment of Huntington's disease. J Neurol 2017;264(12):2457–2463.
19. van Diemen MPJ, Hart EP, Abbruscato A, et al. Safety, pharmacokinetics and pharmacodynamics of SBT-020 in patients with early stage Huntington's disease, a 2-part study. Br J Clin Pharmacol 2021;87(5):2290–2302.
20. Andresen K, Cutting E, Apostolopoulos D, et al. Trial to assess the tolerability of using felodipine to upregulate autophagy as a treatment of Huntington's disease (FELL-HD): a phase II, single-centre, open-label, dose-finding trial protocol. BMJ Open 2024;14(8):e087983.
21. Mochel F, Méneret A, Adanyeguh IM, et al. Effect of Triheptanoin on caudate atrophy and motor scores in patients with early-stage Huntington disease: a phase II study. Neurology 2025;104(2):e210194.
22. Maibach HT, Brownstein MJ, Hersch SM, Anderson KE, Itzkowitz DE, Damiano EM, Simon NG. The vasopressin 1a receptor antagonist SRX246 reduces aggressive behavior in Huntington's disease. J Pers Med 2022;12(10):1561.
23. Brownstein MJ, Simon NG, Long JD, et al. Safety and tolerability of SRX246, a vasopressin 1a antagonist, in irritable Huntington's disease patients-a randomized phase 2 clinical trial. J Clin Med 2020;9(11):3682.
24. Furr Stimming E, Claassen DO, Kayson E, et al. 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. Lancet Neurol 2023;22(6):494–504.
25. Goldberg YP, Navon-Perry L, Cruz-Herranz A, et al. The safety profile of pridopidine, a novel Sigma-1 receptor agonist for the treatment of Huntington's disease. CNS Drugs 2025;39(5):485–498.
26. McColgan P, Thobhani A, Boak L, et al. Tominersen in adults with manifest Huntington's disease. N Engl J Med 2023;389(23):2203–2205.
27. Reilmann R, Feigin A, Rosser AE, et al. Pridopidine in early-stage manifest Huntington's disease: a phase 3 trial. Nat Med 2025;31(11):3780–3789.
28. Travessa AM, Rodrigues FB, Mestre TA, Ferreira JJ. Fifteen years of clinical trials in Huntington's disease: a very low clinical drug development success rate. J Huntingtons Dis 2017;6(2):157–163.
29. Bachoud-Lévi AC. Human fetal cell therapy in Huntington's disease: a randomized, multicenter, phase II trial. Mov Disord 2020;35(8):1323–1335.
30. uniQure Announces Positive Topline Results from Pivotal Phase I/II Study of AMT-130 in Patients with Huntington's Disease (24th September 2025). Available at https://www.uniqure.com/investors-media/press-releases.
31. Tabrizi SJ, Ghosh R, Leavitt BR. Huntingtin lowering strategies for disease modification in Huntington's disease. Neuron 2019;101(5):801–819.
32. Mestre TA. Recent advances in the therapeutic development for Huntington disease. Parkinsonism Relat Disord 2019;59:125–130.
33. Group HS. Effect of Deutetrabenazine on chorea among patients with Huntington disease: a randomized clinical trial. JAMA 2016;316(1):40–50.
34. Cummings J, Zhou Y, Lee G, Zhong K, Fonseca J, Cheng F. Alzheimer's disease drug development pipeline: 2024. Alzheimers Dement (N Y) 2024;10(2):e12465.
35. Boucherie DM, Duarte GS, Machado T, Faustino PR, Sampaio C, Rascol O, Ferreira JJ. Parkinson's disease drug development since 1999: a story of repurposing and relative success. J Parkinsons Dis 2021;11(2):421–429.
36. Petrov D, Mansfield C, Moussy A, Hermine O. ALS clinical trials review: 20 years of failure. Are we any closer to registering a new treatment? Front Aging Neurosci 2017;9:68.
37. Hay M, Thomas DW, Craighead JL, Economides C, Rosenthal J. Clinical development success rates for investigational drugs. Nat Biotechnol 2014;32(1):40–51.
38. Sathe S, Ware J, Levey J, et al. Enroll-HD: an integrated clinical research platform and worldwide observational study for Huntington's disease. Front Neurol 2021;12:667420.
39. PTC518 PIVOT-HD Study Achieves Primary Endpoint; https://ir.ptcbio.com/news-releases/news-release-details/ptc518-pivot-hd-study-achieves-primary-endpoint.
40. Abeyasinghe PM, Long JD, Razi A, et al. Tracking Huntington's disease progression using motor, functional, cognitive, and imaging markers. Mov Disord 2021;36(10):2282–2292.
41. Kinnunen KM, Schwarz AJ, Turner EC, et al. Volumetric MRI-based biomarkers in Huntington's disease: an evidentiary review. Front Neurol 2021;12:712555.

42. Tabrizi SJ, Schobel S, Gantman EC, et al. A biological classification of Huntington's disease: the integrated staging system. Lancet Neurol 2022;21(7):632–644.

43. Long JD, Gantman EC, Mills JA, Vaidya JG, Mansbach A, Tabrizi SJ, Sampaio C. Applying the Huntington's disease integrated staging system (HD-ISS) to observational studies. J Huntingtons Dis 2023;12(1):57–69.

44. Vissers M, Heuberger J, Groeneveld GJ. Targeting for success: demonstrating proof-of-concept with mechanistic early phase clinical pharmacology studies for disease-modification in neurodegenerative disorders. Int J Mol Sci 2021;22(4):1615. https://doi.org/10.3390/ijms22041615.

45. Medina Escobar A, Pringsheim T, Gautreau S, Rivera-Duarte JD, Amorelli G, Cornejo-Olivas M, Rossi M. Epidemiology of Huntington's disease in Latin America: a systematic review and meta-analysis. Mov Disord 2024;39(11):1907–1921.

46. Duy PQ, Sreekrishnan A, David W, et al. Clinical trial publication trends within neurology. Transl Neurosci 2019;10:233–234.

47. Dechartres A, Riveros C, Harroch M, Faber T, Ravaud P. Characteristics and public availability of results of clinical trials on rare diseases registered at clinicaltrials.Gov. JAMA Intern Med 2016;176(4):556–558.

48. Vesper I. Clinical-trial reporting is on the rise. Nature 2024;634:S21–S23.

49. NHS Health Research Authority. Research transparency annual report 2022/23. https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/research-transparency/research-transparency-annual-report-202223/. Last accessed February 7, 2026.

Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.