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Huntington's disease – III. Disease Management and Treatment

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Abstract

There is currently no cure for Huntington's disease (HD) and no treatment proven to delay the onset or slow the progression of the disease but symptoms management, treatment, and support can help reduce some of the problems the disease causes. Management strategies are first discussed including non-invasive therapies, lifestyle adaptations, physiotherapy, pharmacotherapy, and alternative therapies are first discussed.

These are followed by treatment with medicines for movement disorders, mental health conditions including psychotherapy, speech therapy, physical, and occupational therapy. Therapeutic options targeting the disease at its origin are briefly surveyed. Lastly, surgical interventions with deep brain stimulation are mentioned along with participation in clinical trials.

Abbreviations

Cas: CRISPR-associated system; CRISPR: Clustered regularly interspaced short palindromic repeats; CRO: Contract research organization; CT: Clinical trial; CTP: Clinical trial protocol; DBS: Deep brain stimulation; EHDN: European Huntington's Disease Network; EU: European Union; FDA: (U.S.) Food & Drug Administration; Gpe: Globus pallidus externus; HD: Huntington's disease; HDA: Huntington's Disease Association; HTT: Huntington gene; Htt: Huntingtin protein; mHtt: mutant Htt; JHD: Juvenile HD; KA: (U.K.)'s Knowledge-to-Action; mHtt: mutant Htt; OCD: Obsessive–compulsive disorder; PD: Parkinson's disease; PEG: percutaneous endoscopic gastronomy; PEPHD: Patient Education Program for Huntington's Disease; RCT: Randomized CT; RNAi: RNA interference; Snpr: Substantial nigra pars reticulata; SPP: Maelstrom processing peptidase; SSRI: Selective serotonin reuptake inhibitors; STN:

Subtropical nucleus; TALEN: Transcription activator-like effector nuclease; ZFP: Zinc-finger protein.

Keywords

Chorea; Clinical trials; Huntington's disease; Huntington gene; Huntingtin protein; Motor symptoms; Cognitive symptoms; Psychiatric symptoms; Pharmacotherapy; Deep brain stimulation.

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There is currently no cure for Huntington's disease (HD) and no treatment proven to delay the onset or slow the progression of the disease. Living with HD can be very distressing and frustrating for the person with the condition, as well as their loved ones and carers. But, symptoms management, treatment, and support can help reduce some of the problems the disease causes, such as:

• **Medicines:** Certain medications and treatments are available that sometimes help alleviate specific symptoms including depression, mood swings, and involuntary movements.
• **Occupational therapy:** It can help make everyday's tasks easier.
• **Speech and language therapy:** It facilitates feeding and communication problems.
• **Physiotherapy:** It can help with movement and balance.

Professional associations such as the Huntington's Disease Association (HDA) is a useful source of information and support. It offers:

• Information about HD.
• A specialist advisory service.
• Local branches and support groups.
• An online forum.

However, as the disease progresses, the ability to care for oneself declines, and carefully managed multidisciplinary caregiving becomes increasingly necessary. In this Article, I will first discuss non-invasive strategies and life-style adaptations, pharmacotherapy.

Non-invasive strategies

The overall treatment of HD requires a holistic approach to health that involves a range of health professionals. Here, non-invasive strategies and life-style adaptations can play a vital role in the patient's management of HD. Although treatments are available to treat and reduce the severity of some HD symptoms, for many of them, evidence to confirm their effectiveness specifically is incomplete.

Management of problems with dysphagia

Malnutrition is a major issue for HD patients, with the majority having a lower than average body weight. Dietitians can help in these circumstances by providing diet plans and methods to overcome the chorea-induced eating deficits. Such approaches may involve blending foods or providing liquid food substitutes. Alternatively, percutaneous endoscopic gastronomy (PEG) may be performed for some patients in which swallowing is severely affected.

Weight loss and problems in eating due to dysphagia and other muscle discoordination are common, making nutrition management increasingly important as the disease advances. Thickening agents can be added to liquids, as thicker fluids are easier and safer to swallow. Reminding the affected person to eat slowly and to take smaller pieces of food into the mouth may also be of use to prevent choking. If eating becomes too hazardous or uncomfortable, the PEG option is available. This feeding tube, permanently attached through the abdomen into the stomach, reduces the risk of aspirating food and provides better nutritional

management.

Management of motor symptoms and hyperkinetic dysarthria

Chorea being the primary symptom that can severely impair balance and gait, physiotherapists can support patients by extending the proper function of these actions, and assessing when walking aids or wheelchairs are required. Similarly, occupational therapists can assist HD patients through completing home assessments and installing bathroom adaptions or handrails so patients can prolong living in the comfort of their own home.

Patients who exhibit motor symptoms can also develop speech impairments such as hyperkinetic dysarthria, which involves involuntary muscle movements in the mouth, throat, and respiratory system that result in voice hoarseness and abnormal prosody. For these cases, patients can receive speech and language therapy to optimize their verbal communication for as long as possible. If a patient presents with an inability to speak, speech and language therapists can provide communication charts or electronic communicating devices to enable them to continue conversing with friends and family.

Management of psychological and cognitive symptoms

To alleviate the psychological and cognitive symptoms associated with HD, sessions with a psychologist can be used alongside the medications provided. This may not only improve the patient's mental health, but also can be used to monitor how the patient is responding to each medication they are receiving.

Family and caregivers can help create an environment that may help a person with HD manage cognitive and behavioral symptoms, and avoid stressful situations. These strategies include:

• Using calendars and schedules to help keep a regular routine.
• Starting tasks with reminders or assistance.
• Organizing work or activities in order of importance.
• Breaking down tasks into manageable steps.
• Creating an environment that is as calm, simple, and structured as possible.
• Looking for and steering away from stressors that can trigger outbursts, irritability, depression or other symptoms.
• For school-age children or teenagers, talking with school staff to develop an individual education plan.
• Providing chances for the person to maintain social interactions and friendships as much as possible.

Although relatively few studies of exercises and therapies have shown to be helpful to rehabilitate cognitive symptoms of HD, some evidence shows the usefulness of physical therapy, occupational therapy, and speech therapy.

Management of speech-language difficulties

Assessment and management by speech-language pathologists with experience in HD is recommended.

Use of physiotherapy

People with HD may consult with a physical therapist for non-invasive and non-medication-based ways of managing their physical symptoms. These professionals have developed practice guidelines and can issue prescriptions.

- **Development of physiotherapy guidelines**

Physiotherapy guidelines for the management of HD were published in 2020 (Quinn et al. 2020), yet it is not known if physiotherapists are aware of and/or are implementing these guidelines in practice. A small global survey of physiotherapists (Jones et al. 2022) identified the physiotherapist's expertise in HD as one

of a number of facilitators to implementing guidelines in practice. Creative approaches are needed to support physiotherapists to develop expertise in this rare condition. In The U.K., a knowledge-to-Action (KA) study design will be used to develop activities and/or resources that will support physiotherapists in implementing the HD.

- **Physiotherapists activities and prescriptions**

Physical therapists may perform the following activities and issue prescriptions to:

- Implement falls' risk assessment and prevention.
- Implement strengthening, stretching, and cardiovascular exercises. Walking aids may be prescribed as appropriate.
- Prescribe breathing exercises and airway clearance techniques with the development of respiratory problems. Consensus guidelines on physiotherapy in HD have been produced by the European Huntington's Disease Network (EHDN). Goals of early rehabilitation interventions are prevention of loss of function. Participation in rehabilitation programs during the early to middle stage of the disease may be beneficial as it translates into long-term maintenance of motor and functional performance. Rehabilitation during the late stage aims to compensate for motor and functional losses. For long-term independent management, the therapist may develop home exercise programs for appropriate people.

Palliative care

Additionally, an increasing number of people with HD are turning to palliative care, which aims to improve quality of life through the treatment of the symptoms and stress of serious illness, in addition to their other treatments.

Lifestyle and home remedies

Managing HD affects the person with the disease, family members and other in-home caregivers. As the disease gets worse, the person becomes more dependent on caregivers. Several issues need to be addressed, and the ways to cope with them change over time. This begins with education about the disease.

The families of individuals, and society at large, who have inherited or are at-risk of inheriting HD have generations of experience of HD, but may be unaware of recent breakthroughs in understanding the disease, and of the availability of genetic testing (see Article II in this series). Genetic counseling benefits these individuals by updating their knowledge, seeking to dispel any unfounded beliefs that they may have, and helping them consider their future options and plans.

The HDA has created a Patient Education Program for Huntington's Disease (PEPHD) to help educate family members, caretakers, and those diagnosed with HD, including information concerning family planning choices, care management, and related considerations.

Eating and nutrition

Factors regarding eating and nutrition include the following:

• **Trouble maintaining a healthy body weight:** This may be caused by having trouble eating or by needing more calories due to physical exertion or a metabolic condition. To get enough nutrition, one may need to eat more than three meals a day or use dietary supplements.
• **Trouble with chewing, swallowing, and fine motor skills:** This can limit the amount of food one eats and increases the risk of choking. It may help to remove distractions during a meal and select foods that are

easier to eat. Utensils designed for people with limited fine motor skills and covered cups with straws or drinking spouts also can help. Eventually, a person with HD needs help with eating and drinking.

Keeping active with Huntington's disease

The Huntington's Disease Association (HDA) resource provides information and tips & hints on how to make a physical activity plan that is unique for a person with HD. The resource was developed by researchers at Cardiff University, the HDA of England and Wales, Carer's Trust Wales, and carers and people with HD.

Pharmacotherapy

In 2000, in the European Union (EU), *Tetrabenazine* was approved for the treatment of chorea in HD, and in 2008 in the U.S. Although other drugs had been used "off label", Tetrabenazine was the first approved treatment for HD in the U.S. The compound has been known since the 1950s. An alternative to Tetrabenazine is *Amantadine* but there is limited evidence for its safety and efficacy. Other drugs that help to reduce chorea include antipsychotics and *Benzodiazepines*.

Hypokinesia and rigidity, especially in juvenile cases, can be treated with antiparkinsonian drugs, and myoclonic hyperkinesia can be treated with *Valproic acid.* There is tentative evidence for *Ethyl eicosapentaenoic* acid to improve motor symptoms at one year. In 2017, the FDA approved *Deutetrabenazine* (marketed as Austedo), a heavier form of Tetrabenazine medication for the treatment of chorea in HD.

Psychiatric symptoms can be treated with medications similar to those used in the general population. *Selective serotonin reuptake inhibitors* (SSRI) and Mirtazapine have been recommended for depression, while atypical antipsychotics are recommended for psychosis and behavioral problems. Specialist neuropsychiatric input is recommended since people may require long-term treatment with multiple medications in combination.

Alternative therapies

A number of alternative therapies have been experimented in ayurvedic medicine with plant-based products, although none have provided good evidence of efficacy. A recent study showed that the stromal processing peptidase (SPP), a synthetic enzyme found in plant chloroplasts, prevented the aggregation of proteins associated with HD. However, repeat studies and clinical validation are needed to confirm its true therapeutic potential.

Treatment

There is currently no cure or treatment which can halt, slow or reverse the progression of the disease. However, there are many treatments and interventions that can help to manage HD symptoms:

• **A neurologist, psychiatrist, or nurse with expertise in HD:** May prescribe medications to ease anxiety and depression, help with troublesome behaviors, and calm uncontrolled movements.

• **A psychologist or social worker:** Can provide individual or group counseling.

• **Physical and occupational therapists:** Can work with patients and families to develop strength, move safely, and adjust the home environment and activities as needed.

• **Speech language pathologists and nutritionists:** Can help with communication, eating and swallowing safely, and combating weight loss.

• **Clinician researchers:** May suggest participation in

HD clinical trials.

• **Social and community support:** This is an important former responsibilities and help with daily activities and care routines when they can no longer do so themselves. Caregivers and kids may also need support for the challenges and stresses that come with HD.

Medicines

Medicines can lessen some symptoms of movement and mental health conditions. Multiple interventions can also help a person adapt to changes in abilities for a certain amount of time. It is important to note that the medicines taken may change over the course of the disease, depending on the overall treatment goals. Also, medicines that treat some symptoms may result in side effects that worsen other symptoms. Treatment goals should be regularly reviewed and updated.

The most commonly prescribed HD medications are targeted to reduce chorea. One of the major pathological hallmarks of HD is the degeneration of the basal ganglia and particularly the striatum, which has been linked to the development of chorea (see Article I in this series).

The basal ganglia contributes to the initiation of movement and suppression of unwanted movements. Refinement of movement by basal ganglia structures occur through the direct and indirect pathways. In HD, it is hypothesized that the early loss of the enkephalin-containing medium spiny neurons results in reduced inhibition of the globus pallidus externus (GPe) and, therefore, increased inhibition of the subthalamic nucleus (STN).

This, in turn, leads to decreased activation of the GPe

part of HD care. Family, friends, loved ones, and companions often assume many of the HD person's

and the substantia nigra pars reticulata (Snpr), resulting in decreased inhibition of the thalamus. An increase in the resulting excitation of the cortex through excitatory thalmo-cortical projections can lead to excess uncontrolled movements causing chorea. Although, chorea is the hallmark symptom of HD, affective and cognitive symptoms can be observed decades before the onset of chorea.

- **Medicines for movement disorders: Medicines to treat movement disorders include (Table 1):**

◦ **Movement disorders control:** They include Tetrabenazine (Xenazine), Deutetrabenazine (Austedo) and Valbenazine (Ingrezza). They have been approved by the (U.S.) Food and Drug Administration (FDA) to suppress involuntary jerking and writhing movements, known as chorea. Other chorea suppressants include Amantadine (Gocovri), Levetiracetam (Keppra, Spritam) and Clonazepam (Klonopin). However, these medicines do not affect how the disease progresses. Mild effectiveness and side effects may limit their use. Possible side effects include drowsiness, restlessness, and the risk of worsening or triggering depression or other psychiatric conditions.

◦ **Antipsychosis:** They include Haloperidol, Fluphenazine, Olanzapine (Zyprexa), and Aripiprazole (Abilify, Aristada), which have the side effect of suppressing movements and may help to treat chorea. However, these medicines may worsen involuntary muscle contractions called dystonia and cause slowness of movements, resembling Parkinson's disease (PD). They also may cause restlessness and drowsiness.

Purpose	Medicines	Side effects or risks
Movement disorders control	o Amantadine (Gocovri) o Clonazepam (Klonopin) o Deutetrabenazine (Austedo) o Levetiracetam (Keppra, Spritam) o Tetrabenazine (Xenazine) o Valbenazine (Ingrezza)	o Depression o Drowsiness o Recklessness o Other psychiatric conditions
Antipsychosis	o Aripiprazole (Abilify, Aristada) o Fluphenazine o Haloperidol o Olanzapine (Zyprexa)	o Drowsiness o Dystonia worsening o Movements slowness o Movements suppression o Restlessness

Table 1: Medicines for movement disorders

- **Medicines for mental health conditions: Medicines to treat mental health vary depending on the conditions and symptoms. Possible treatments include (Table 2):**

• **Antidepressants:** They include Citalopram (Celexa), Escitalopram (Lexapro), Fluoxetine (Prozac) and Sertraline (Zoloft). These medicines also may have some effect on obsessive-compulsive disorder (OCD) symptoms. Side effects may include nausea, diarrhea, drowsiness and low blood pressure.

• **Antipsychotics:** These include Quetiapine (Seroquel) and Olanzapine (Zyprexa), which may suppress violent outbursts, agitation, and other symptoms. However, these medicines may cause different movement disorders themselves.

• **Mood stabilizers:** They can help prevent the highs and lows associated with bipolar disorder. They include anti-seizure medicines such as Divalproex (Depakote), Carbamazepine (Tegretol, Carbatrol, Epitol, others) and Lamotrigine (Lamictal).

Purpose	Medicines	Side effects or risks
Antidepressants	o Citalopram (Celexa) o Escitalopram (Lexapro) o Fluoxetine (Prozac) o Sertraline (Zoloft)	o Diarrhea o Drowsiness o Effect on OCD symptoms o Low blood pressure o Nausea
Antipsychotics	o Quetiapine (Seroquel) o Olanzapine (Zyprexa)	o Different movement disorders
Mood stabilizers	o Anti-seizures o Carbamazepine (Tegretol, Carbatrol, Epitol, others) o Divalproex (Depakote) o Lamotrigine (Lamictal).	o Prevent highs/lows of bipolar disorder

Table 2: Medicines for mental health conditions

The action mechanisms for currently used medications for HD treatment are set forth in Table 3 below:

Medication class	Medication	Action mechanism
Chorea medication	o Tetrabenazine o Deutetrabenazine	o Depletes central monoamines by reversibly inhibiting VMAT2. o Depletes central monoamines by reversibly inhibiting VMAT2, however, has a longer half-life.
Antipsychotic medication	o Olanzapine o Risperidone	o Inhibits dopamine receptors, serotonin receptors, histamine receptors as well as a1-adrenergic and muscarinic receptors. o Selectively inhibits serotonin and dopamine-D2 receptors.
Antidepressants (SSRIs)	o Citalopram o Fluoxetine o Sertraline	o Inhibits the reuptake of 5-HT into the presynaptic nerve terminal. o Inhibits the reuptake of 5-HT into the presynaptic nerve terminal. o Inhibits the reuptake of 5-HT into the presynaptic nerve terminal.
Mood stabilizers	o Lamotrigine o Carbamazepine	o Blocks voltage-gated sodium ion channels; also suppresses excitatory neurotransmitters glutamate and aspartate. o Blocks voltage-gated sodium ion channels.

Ref: Mackenzie, Ferguson, Connor et al., 2022.

Table 3: Currently used medications for HD treatment and mechanisms of action

Psychotherapy

A psychotherapist — a psychiatrist, psychologist, or clinical social worker — can provide talk therapy to help with behavioral symptoms. The psychotherapist can help the patient and his or her family develop coping strategies, manage expectations as the disease gets worse, and help family members communicate.

Speech therapy

HD can affect the control of muscles of the mouth and throat that are essential for speech, eating, and swallowing. A speech therapist can help improve the ability to speak clearly or teach how to use communication devices. A communication device might be as simple as a board covered with pictures of everyday items and activities. Speech therapists also can address trouble with eating and swallowing.

Physical therapy

A physical therapist can teach proper and safe exercises that enhance strength, flexibility, balance, and coordination. These exercises can help maintain mobility as long as possible and may reduce the risk of falls. Instruction on posture and the use of supports to improve posture may help lessen some movement symptoms. When a walker or wheelchair is needed, the physical therapist can advise on the proper use of the device and posture. Also, exercises can be adapted for the level of mobility.

Occupational therapy

An occupational therapist can assist the patient, family members, and caregivers on how to use assistive devices to improve function. These strategies may include:

• Handrails at home.
• Assistive devices for activities such as bathing and dressing.
• Eating and drinking utensils adapted for people with limited fine motor skills.

Therapeutic options targeting the disease at its origin

As discussed in the previous sections, the current therapies prescribed for HD can be categorized by the symptom(s) they treat. These categories include chorea medication, antipsychotic medication, anti-depressants, mood stabilizing medication as well as non-drug therapies.

Fortunately, there are also many new HD therapeutics currently undergoing clinical trials that target the disease at its origin by lowering the levels of mutant huntingtin protein (mHtt). Presently, much attention is being directed to:

- Antisense oligonucleotide (ASO) therapies: They bind to pre-RNA or mRNA and can alter protein expression via RNA degradation;
- Blocking translation;
- Splice modulation;
- RNA interference (RNAi) therapies;
- RNA targeting small molecule therapies;
- Stem cell therapies;
- Antibody therapies;
- Non-RNA targeting small molecule therapies; and
- Neuroinflammation targeted therapies.

Potential therapies in pre-clinical development include:

- Zinc-Finger Protein (ZFP) therapies;
- Transcription activator-like effector nuclease (TALEN) therapies; and
- Clustered regularly interspaced short palindromic repeats (CRISPR)/CRISPR-associated system (Cas) therapies.

(For details regarding the current status of the corresponding clinical trials, the administration of the drugs, their allele specificity, and the dosing frequency, the reader is referred to Mackenzie, Ferguson, Connor et al., 2022.)

Surgical treatments

An alternative surgical treatment is deep brain stimulation (DBS). This intervention is primarily used to improve chorea symptoms. A study from Gonzalez et al. (2014) found DBS to be effective at reducing chorea in pharmacologically-resistant chorea HD patients. It did not, however, reduce dystonia or bradykinesia. As pharmacological-resistant HD is rare, the use of this intervention is rare. The infrequent use of this treatment can also be attributed to the additional risks associated with the invasive procedure.

Overall, treatment of HD should not solely be the clinician's responsibility and the medications they prescribe. For optimal treatment, a range of health care professionals should be involved with an extensive network of communication between them.

Participation in clinical trials

On clinical trials and research studies

People with Huntington's disease (HD) may be able to take part in clinical trials. Healthy people with no HD problems and no family history of such conditions may also be able to participate. Joining a clinical trial or other research study is also a way to help fight such issues. To find out more about clinical trials:

- Check out www.ClinicalTrials.gov.
- See "NIH Clinical Research Trials and You" at www.nih.gov/health/clinicaltrials. This is a resource for people who want to learn more about clinical trials.
- EVisit the various support institutions described in Chapter 19.

In the Sidebar, I provide the main particulars of clinical trials. The following sections will briefly set forth the particulars and aims of 100 such trials on HD, which have been extracted from the 258 clinical trials indicated on clinicaltrials.gov website as of the date of this writing (1 August 2024). Irrespective of its status, any trial having submitted results could be of interest to HD patients, their families, and carers if appropriate for the patient's medical condition. (For more details on any of these and other trials, the reader is referred to the above website.)

Questions usually asked by potential HD participants

• **Can a HD patient participate in a clinical trial?** Yes, and it is encouraged for those eligible participants. The best way to find out about trials and to express interest in participating in one of them is to be referred by one's own neurologist or physician. That healthcare professional will be able to identify possible suitable trials for the existing medical condition, make a referral, and facilitate the enrollment process, as appropriate.

• **Is the list of clinical trials available?** It can be found on line: www.clinicaltrials.gov. This site lists all registered trials across the world and their status: New [N], Recruiting [R], Not Yet Recruiting [NYR], Not Recruiting [NR]; Enrolling By Invitation [EBI]; Completed [C], [CWR] Completed With Results, Suspended [S], Terminated [T], Unknown [U], or Withdrawn [W].

• **Does it cost anything to participate in a clinical trial?** Participation is usually free.

Currently recruiting clinical trials

The number of clinical trials that are currently recruiting may vary depending on the particular date at which the website clinicaltrials.gov is searched. On 1 August 2024, that number was 258, of which only the first 48 fell into the following categories: Registry (1); biomarkers (1), cognitive pretesting (1), pharmacotherapeutic treatment (30), neurodevelopment (1), neuroprotection (1), cognition (3), therapeutic development (1), gene therapy treatment (2), deep brain stimulation (2), working memory (1), exercise (2), music therapy (1), costs (1).

Current research trends and future outlook

Positive steps are being made in the development of current HD therapeutics. Guidance for clinicians on HD treatment is improving with guidelines recently released to elevate international standards of HD care.

Current therapies focus on symptom management via multidisciplinary teams, using pharmacological and non-pharmacological treatment. However, HD management has not significantly advanced for the past 20 years. Furthermore, diverse and changeable symptom presentations create complexity when treating HD. There is no cure for HD, or therapeutic to alter the disease onset or progression. HD management requires a tailored approach not only due to symptom diversity, but also adverse effects, common contraindications, drug-drug interactions, and certain HD medications worsening other symptoms. Clinicians must navigate these issues in addition to effectively treating HD symptoms.

Perhaps the most prominent shortcoming of today's HD therapeutics and previous experimental therapeutics is their inability to impact specific HD targets, instead influencing non-specific and downstream processes. This limits their efficiency as disease mechanisms will still propagate and cause harm where they are not inhibited. Pursuing HD-specific targets at the root cause of disease is therefore the new and likely future research direction. The recent surge in interest to develop therapies that target mHTT RNA and DNA shows this trend. Additional therapeutic targets are

being investigated, including dopaminergic and glutamatergic neurotransmission, synaptic activity, BDNF signaling, mitochondrial function and biogenics, and aggregate inhibition. However, several of these targets were primarily researched over 10 years ago, and do not appear to be currently areas of significant interest in the field. Peripheral targets are also being investigated due to peripheral HD symptoms and HTT expression. For example, the gut microbiome is a key target due to its bidirectional communication with the brain and alteration in HD.

RNA targeting therapies, particularly antisense oligonucleotides, have favorable results and are currently one of the most promising future HD therapeutics. However, they come with their own challenges. It is unknown whether non-selective HTT lowering is safe, if off-target effects will occur in larger populations, whether mHTT is the singular cause of HD pathology, and if permanent HTT suppression is required. Furthermore, if allele-specific treatments are required, SNP will not treat all HD patients.Many RNA based therapies also require invasive administration. Whether this is tolerable and effective in the long term for larger populations will likely be determined by future research. Initial clinical findings from RNAi therapies and RNA targeting small molecules, and further clinical results from antisense oligonucleotides will clarify RNA based therapies' efficacy for HD patients. Particularly, results of larger trials such as PRECISION-HD1 and PRECISION-HD2, and further information on GENERATION-HD1 will likely inform whether antisense oligonucleotides remain the frontrunners of future HD therapeutics.

DNA therapies may also enter clinical trials within the next decade, but much work still needs to be done to achieve this goal. Ensuring DNA therapies, particularly CRISPR therapies, are safe for human use will be of primary importance. Combination therapies may also be explored in future research. Current research suggests combining multiple RNA targeting therapies, or RNA targeting therapies with antibodies or stem cells may be beneficial.

Work on future HD therapeutics will continue for numerous years to come and resulting treatments for HD patients are likely some time away. However, many of the latest developments are encouraging and a new era of HD therapeutics may be approaching.

Conclusions and take-aways

- There is currently no cure for HD and no treatment proven to delay the onset or slow the progression of the disease. But, treatment and support can help reduce some of the problems it causes.
- Treatments are available to treat and reduce the severity of some HD symptoms. However, for many of these treatments, evidence to confirm their effectiveness is incomplete. Some evidence shows the usefulness of physical therapy, occupational therapy, and speech therapy.
- Advice and tips have ben provided regarding the management of cognitive and mental health conditions including problems with dysphagia, speech language therapy, physical therapy, palliative care, and pharmacotherapy (prescription drugs and plant-based supplements), lifestyle and home remedies, and keeping active with Huntington's disease.
- Medicines for movement disorders and mental health conditions have been reviewed and conveniently tabulated.
- The benefits of psychotherapy, speech therapy, physical therapy, and occupational therapy have been set forth.

- New HD therapeutics are currently undergoing clinical trials that target the disease at its origin lowering the levels of mutant huntingtin protein (mHtt). Presently, much attention is being directed to: Antisense oligonucleotide therapies, blocking translation, splice modulation, RNA interference therapies, RNA targeting small molecule therapies, stem cell therapies, antibody therapies, non-RNA targeting small molecule therapies, and neuroinflammation targeted therapies.

- Potential therapies in pre-clinical development include: Zinc-finger protein therapies, transcription activator-like effector nuclease therapies, and clustered regularly interspaced short palindromic repeats and associated system therapies.

- Clinical trials are prospective biomedical or biobehavioral research studies on human participants designed to answer specific questions about biomedical or biobehavioral interventions, including new treatments (such as novel vaccines, drugs, dietary choices, dietary supplements, and medical devices) and known interventions that warrant further study and comparison. Their overriding goal is to determine if a new test or treatment works and is safe.

- People with Huntington's disease problems may be able to take part in clinical trials. Healthy people with no such disease problems and no family history of such conditions may also be able to participate. Joining a clinical trial or other research study is also a way to help fight such issues.

- The Huntington's Disease TrialFinder is a clinical trials matching service of the Huntington's Disease Society of America (HDSA). It is a way for individuals with HD, caregivers, healthy volunteers, and physicians to connect with current research studies.

- A sidebar provides a brief primer on clinical trials: Nature; overall goal(s), design and objective(s); use of the data generated; categorization (drugs, devices, procedures); types by research objectives or research purposes (prevention, screening, diagnostic, treatment, quality of life or supportive care, genetic, epidemiological, compassionate use or expanded access, fixed, or adaptive). It also describes the various trial phases.

Sidebar – A brief primer on clinical trials

Clinical trials (CTs) are prospective biomedical or biobehavioral research studies on human participants designed to answer specific questions about biomedical or biobehavioral interventions, including new treatments (such as novel vaccines, drugs, dietary choices, dietary supplements, and medical devices) and known interventions that warrant further study and comparison. They are part of clinical research at the heart of all medical advances. They look at new ways to prevent, detect, or treat diseases by new drugs or new combinations of drugs, new surgical procedures or devices, or new ways to use existing treatments. They can also look at other aspects of care, such as improving the quality of life for people with chronic illnesses. Their goal is to determine if a new test or treatment is safe and effective. Some CTs involve healthy subjects with no pre-existing medical conditions, others pertain to people with specific health conditions who are willing to try an experimental treatment. Pilot experiments are conducted to gain insights for design of the CTs to follow.

Except for small, single-location trials, the design and

objectives are specified in a document called a clinical trial protocol (CTP). This is the trial's "operating manual" to ensure that all researchers perform the trial in the same way on similar subjects, and that the data is comparable across all subjects. As a trial is designed to test hypotheses and rigorously monitor and assess outcomes, it can be seen as an application of the scientific method, specifically the experimental step.

CTs generate data on dosage, safety, and efficacy. They are conducted only after they have received regulatory approval (ethics committee approval and health authority), which vet the risk/benefit ratio of the trial and allow or deny it.

Depending on product type and development stage, investigators initially enroll volunteers or patients into small pilot studies, and subsequently conduct progressively larger-scale comparative studies.

CTs can vary in size and cost, and can involve a single research center or multiple centers, in one or in multiple countries. The clinical study design aims to ensure the scientific validity and reproducibility of the results. Costs for clinical trials can range into the billions of dollars per approved drug. The sponsor may be a governmental organization or a pharmaceutical, biotechnology, or medical device company. Certain functions necessary to the trial, such as monitoring and laboratory work, may be managed by an outsourced partner, such as a contract research organization (CRO) or a central laboratory. Only 10% of all drugs started in human clinical trials become approved drugs.

Overall goals

There are two goals to testing medical treatments: To learn whether they work well enough, called "efficacy" or "effectiveness"; and to learn whether they are safe enough, called "safety". Neither is an absolute criterion and both safety and efficacy are evaluated relative to how the treatment is intended to be used, what other treatments are available, and the severity of the disease or condition. The benefits must outweigh the risks.

The sponsor designs the trial in coordination with a panel of expert clinical investigators who also consider what alternative or existing treatments exist to compare to the new drug and what type(s) of patients might benefit.

Categories of trials

There are three trial categories:

• **Drugs:** They are the most common to evaluate new pharmaceutical products, biologics, diagnostic assays, psychological therapies, or other interventions.
• **Devices:** Similarly to drugs, manufacturers of medical devices may compare a new device to an established therapy, or may compare similar devices to each other. They are required for pre-market approval.
• **Procedures:** Similarly to drugs, medical or surgical procedures may be subjected to clinical trials, They compare different surgical approaches in treatment.

Types of trials

CTs are classified by the research objective(s) or purpose(s) of the investigators:

• **By research objectives:** This will depend on the kind of study. Thus, in an:

◦ **Observational study:** The investigators observe the subjects and measure their outcomes. They do not actively manage the study.
◦ **Interventional study:** The investigators give the research subjects an experimental drug, use of a medical device, a surgical procedure, diagnostic or other intervention to compare the treated subjects with those receiving no treatment or the standard treatment. Then, the researchers assess how the subjects' health changes.

• By research purposes: There are ten such types:

◦ **Prevention trials:** They look for ways to prevent disease in people who have never had the disease or to prevent a disease from returning. These approaches may include drugs, vitamins or other micronutrients, vaccines, or lifestyle changes.

◦ **Screening trials:** They test for ways to identify certain diseases or health conditions.

◦ **Diagnostic trials:** They are conducted to find better tests or procedures for diagnosing a particular disease or condition.

◦ **Treatment trials:** They test experimental drugs, new combinations of drugs, or new approaches to surgery or radiation therapy.

◦ **Quality-of-life trials or supportive care trials:** They evaluate how to improve comfort and quality of care for people with a chronic illness.

◦ **Genetic trials:** They are conducted to assess the prediction accuracy of genetic disorders making a person more or less likely to develop a disease.

◦ **Epidemiological trials:** They have the goal of identifying the general causes, patterns or control(s) of diseases in large numbers of people.

◦ **Compassionate use trials or expanded access trials:** They provide partially tested, unapproved therapeutics to a small number of patients who have no other realistic options. Usually, this involves a disease for which no effective therapy has been approved, or a patient who has already failed all standard treatments and whose health is too compromised to qualify for participation in randomized clinical trials (RCTs). Usually in the U.S., case-by-case approval must be granted by both the FDA and the pharmaceutical company for such exceptions.

◦ **Fixed trials:** They consider existing data only during the trial's design, do not modify the trial after it begins, and do not assess the results until the study is completed.

◦ **Adaptive trials:** They use existing data to design the trial, and then use interim results to modify the trial as it proceeds. Modifications include dosage, sample size, drug undergoing trial, patient selection criteria, and "cocktail" mix.

Trial phases

CTs are conducted typically in four phases (Phases I to IV), with each phase using different numbers of subjects and having a different purpose to construct focus on identifying a specific effect. However, for new drugs, there are five phases (Phases 0 and I to IV), each phase being treated as a separate CT. Table 4 recapitulates the aims of these phases:

Phase	Aim	Notes
0	**Pharmacodynamics** (what the drug does to the body). **Pharmacokinetics** (what the body does or how it reacts to the drug) in humans.	o Optional. o Sub-therapeutic doses. o Small number of subjects (10-15) for preliminary data. o Trial documents the absorption, distribution, metabolization, and clearance (excretion) of the drug, and the drug's interactions within the body, to confirm that these appear to be as expected.
I	**Safety**	o Small number of subjects (20-30). o Determines safe dosage ranges. o Identifies side effects.
II	**IIa. Dosing** **IIb. Efficacy**	o IIa: Dosing requirements. o IIb: Efficacy to establish therapeutic dose range.

III	**Confirmation of safety and efficacy**	o Large group of subjects (1,000-3,000). o Monitors side effects. o Compares to commonly-used treatments.
IV	**Post-marketing safety**	o Delineates benefits, risks, optimal use. o Ongoing during the drug's lifetime of active medical use.

Reference: Wikipedia

Table 4: Phases of clinical trials

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