HUNTINGTON'S DISEASE

CHI Formulary Indication Review

مجلس الضمان الصحي
Council of Health Insurance

October 2023

Table of Contents

Related Documents

Related SOPs

- IDF-FR-P-02-01-IndicationsReview&IDFUpdates
- IDF-FR-P-05-01-UpdatedIndicationReview&IDFUpdates

Related WI:

- IDF-FR-WI-01-01SearchMethodologyGuideForNewIndications

List of Tables

List of Figures

Abbreviations

ADL	Activities of Daily Living
AE	Adverse Effect
CADTH	Canadian Agency for Drugs and Technologies in Health
CAG	Cytosine, Adenine, and Guanine Trinucleotide
CHI	Council for Health Insurance
ECT	Electroconvulsive Therapy
EMA	European Medicines Agency
FDA	US Food and Drug Administration
HAS	Haute Autorité de Santé
HCP	Healthcare Professional
HD	Huntington's Disease
HTT	Huntingtin Gene
IQWIG	Institute for Quality and Efficiency in Healthcare
MD	Medical Doctor
mMS	modified Motor Score
NICE	National Institute for Health and Care Excellence
OCD	Obsessive Compulsive Disorder
OT	Occupational Therapist
PBAC	Pharmaceutical Benefits Advisory Committee
PRN	Pro Re Nata (As Needed)
PT	Physical Therapist
SLP	Speech Language Pathologist
SSRI	Selective Serotonin Reuptake Inhibitor
STD	Sexually Transmitted Disease
TBZ	Tetrabenazine
TMS	Total Motor Score
UHDRS	Unified Huntington's Disease Rating Scale

Executive Summary

Huntington's disease (HD), a neurodegenerative autosomal dominant disorder, is characterized by a triad of **movement** (involuntary **choreatic** movements – spasmodic involuntary movements of the limbs or facial muscles), **cognitive** and **behavioral** disturbances. Its etiology is associated with cytosine, adenine, and guanine (CAG) trinucleotide repeats on the short arm of chromosome 4p16.3 in the Huntingtin (HTT) gene. This mutation leads to an abnormally long expansion of the polyglutamine in the HTT protein, which leads to neurodegeneration. HD commonly affects patients between the ages of 30 to 50 years. However, the longer the CAG repeats, the earlier the onset of symptoms. The term juvenile HD refers to the onset of illness before the age of 20 and is characterized by learning difficulties as well as behavioral disturbances[1].

Huntington's disease has a worldwide pooled incidence of 0.48 cases per 100,000 person-years. Subgroup analysis by continent demonstrated a significantly higher incidence of HD in Europe and North America than in Asia. In addition, pooled prevalence was 4.88 per 100,000. Subgroup analysis by continent demonstrated that the prevalence of HD was significantly higher in Europe and North America than in Africa[2]. There have been no issued recent updates on the incidence and prevalence of HD in Saudi Arabia; however, a recent study from Oman showed a prevalence of 7.36 per 100 000[3].

A clinical diagnosis can be established when a patient exhibits motor and/or cognitive and behavioral issues and has a parent already diagnosed with Huntington's disease. Verification of this diagnosis can be achieved through DNA testing. In individuals who are at risk of inheriting the disease, a pre-symptomatic diagnosis can ascertain whether they carry the mutated gene. The signs and symptoms classically consist of motor, cognitive, and psychiatric disturbances. Secondary symptoms include ataxia, gait abnormalities, eye movement impairment and seizures. Other less common features include weight loss, sleep disturbances, and autonomic nervous system dysfunction. From the onset of symptoms, people with HD have a life expectancy of 10 to 25 years[1].

Figure 1 is retrieved from a position paper on the biological classification of Huntington's Disease and depicts the genetic continuum of HD[4]:

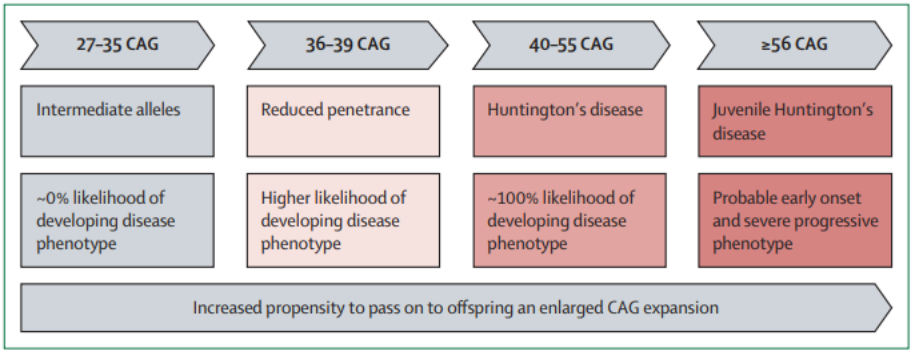


Figure 1. *The Genetic Continuum of Huntington's Disease*

The goal of HD management is mainly aimed at enhancing the patients' quality of life, preventing disease progression, and preventing the development of potential complications. There exists a wide range of complications associated with HD; these include a shortened lifespan, injury and poor positioning or immobility as well as mental distress to the patient and caregivers[1]. The two leading causes of death attributed to HD include pneumonia and cardiovascular diseases (myocardial infarction/degeneration, congestive heart failure…)[5].

This report compiles all clinical and economic evidence related to Huntington's disease according to the relevant sources. The ultimate objective of issuing HD guidelines by the Council of Health Insurance is to update the IDF (CHI Drug Formulary) with **the best available clinical and economic evidence related to drug therapies, ensuring timely and safe access to HD patients in Saudi Arabia**. The main focus of the review was on North American, European and International guidelines. To elaborate, all guidelines drew focus on symptomatic and supportive care for potential complications and comorbidities associated with HD in adults and children. In addition, recent systematic reviews and meta-analysis were tackled; thereby providing an in-depth understanding of HD characteristics.

The management of Huntington's Disease involves a **multidisciplinary approach**. Although the treatment of HD is not curative, effective therapeutic approaches exist for **symptomatic management** with the aim of enhancing the quality of life, as there are no disease-modifying therapies yet available. The treatment approaches may be pharmacological (dopamine antagonists, benzodiazepines, acetylcholinesterase, lithium, and glutamate antagonists) or non-pharmacological (deep brain stimulation, nutritional support, and physical therapy). These measures typically address the hyperkinetic movement disorders associated with HD, such as chorea, dystonia, and myoclonus. Adjunctive therapies, as well as behavioral plans and cognitive interventions may also play a role and should be considered. Several promising novel therapies are currently in the pipeline for the management of HD. These include gene therapies as AMT-130 and other pharmaceutical agents as

SOM3355 (Bevantolol Hydrochloride), Pridopidine, Tominersen, PTC518, Sage-718, ANX-005, PEPINEMAB/VX15, SRX246, Triheptanoin, Dextromethorphan/Quinidine, Long-term IV injection of stem cells, Resveratrol, Nilotinib, INT41, P110, Small hairpin-RNA, Zinc finger nucleases, Anti-sense oligonucleotide, and EHP-102[6]. AMT-130 is a one-time gene therapy. It contains a microRNA (or miRNA) that targets the mutant huntingtin gene. When infused into the patient's brain, the miRNA can direct cellular machinery to cut up RNA encoding mutant huntingtin, with the goal of making the RNA unusable and reducing the amount of mutant protein accumulating in the neurons[7].

All recommendations are well supported by reference guidelines, Grade of Recommendation (GoR), Level of Evidence (LoE) and Strength of Agreement (SoA) reflecting specific drug class role in the management of Huntington's Disease.

Major recommendations for suggested drug therapies are summarized in table 1.

The report mainly tackles pharmacological treatment options for complications or comorbidities associated with HD; specifically chorea. There are **no SFDA registered drugs** for the management of Huntington's disease.

Table 1. Non-SFDA Registered Drugs for the Management of Huntington's Disease

Medication	Indication	Line of Therapy	Level of Evidence/ Recommendation
Tetrabenazine	Chorea Associated with HD	1st line	Strong Recommendation[8]
Deutetrabenazine	Chorea Associated with HD	Alternative therapy	Strong Recommendation[9]
Valbenazine	Chorea Associated with HD	Alternative therapy	Strong Recommendation[10]

Tetrabenazine, deutetrabenazine, and valbenazine belong to the class of vesicular monoamine transporter type 2 (VMAT2) inhibitors. Inhibition of VMAT2 reduces dopamine storage and release. Diminishing dopamine release in turn curtails the hypothetical overstimulation of supersensitive D2 dopamine receptors in the motor striatum that causes tardive dyskinesia. Trimming dopamine release via VMAT2 inhibition in the motor striatum results in stronger "stop" signals and weaker "go," signals and thus robust therapeutic effects in reducing the abnormal involuntary hyperkinetic movements of tardive dyskinesia[11].

Other potentially beneficial agents for the management of Chorea associated with HD include second-generation antipsychotics and off-label use of neuroleptics among other agents.

The report concludes with the addition of a key recommendation synthesis section, which emphasizes the utilization of each drug class for specific patient groups.

Section 1.0 Summary of Reviewed Clinical Guidelines and Evidence

1.1 KSA Guidelines

To date, there are no available guidelines issued by Saudi bodies for the management of Huntington's Disease.

1.2 International Guidelines

1.2.1 International Guidelines for the Treatment of Huntington's Disease [2019]

The European Huntington's Disease Network (EHDN) commissioned an international task force to provide global evidence-based recommendations for everyday clinical practice for treatment of Huntington's disease[12]; the following grading of recommendations was opted:

Table 2. EHDN Level of Scientific Evidence and Gradation of Studies

Level of Scientific Proof Provided by the Study	Quality Grade
Level 1 • Meta-analyses of randomized controlled trials • Randomized controlled trials of high power	**A** Established scientific proof
Level 2 • Randomized controlled trials of low power • Properly conducted non-randomized • controlled trials • Cohort studies	**B** Scientific presumption
Level 3 • Case-control studies	**C** Low-level of scientific proof
Level 4 • Comparative studies with major bias	

• Case series	

The recommendations are detailed below:

Management of Chorea

- **Tetrabenazine** is a first line agent for the management of chorea. **(Grade A)**
- Second generation neuroleptics are first-line treatments in patients who have associated personality and/or behavioral or psychotic disorders. **(Grade B)**
- Monotherapy to treat chorea is preferred because combination therapy increases the risk of adverse effects and may complicate the management of non-motor symptoms.
- In the presence of disturbing chorea, appropriate protective measures (especially during mealtimes and during the performance of instrumental activities of daily living) should be put in place to avoid traumatic injury or choking.
- Rehabilitation specialists can help identify appropriate assistive technology devices and positioning techniques.

Management of Dystonia

- Both active and passive physiotherapy approaches are recommended as a preventive measure to maintain the range of joint motion, limit postural and musculoskeletal deformities, and prevent the development of contractures.
- Injection of botulinum toxin in the case of focal dystonia or to prevent secondary deformities should be performed by a trained professional.
- Customized chairs can provide a comfortable environment in view of dystonia-related deformities.

Rigidity

- Rigidity may be increased or induced by the use of neuroleptics or tetrabenazine.
- If this impacts the functional capacity of the patient, a reduction in dosage or the withdrawal of neuroleptics and/or tetrabenazine should be considered.
- Levodopa may provide partial and temporary relief of the akinetic–rigid symptoms of HD, especially in juvenile forms. **(Grade C)**
- Physiotherapy is recommended to improve or maintain mobility and prevent the development of contractures and joint deformity. **(Grade C)**

Akathisia

- Tetrabenazine, neuroleptics and SSRIs may cause akathisia in HD and reducing the dose or changing the treatment may be helpful. **(Grade C)**

Myoclonus

- Treatment with sodium valproate or clonazepam, used alone or in combination, and in escalating doses, is recommended for the treatment of myoclonus. **(Grade C)**
- Levetiracetam is a therapeutic alternative for the same indication.
- In case of myoclonus of cortical origin that is not associated with epileptic seizures, piracetam has a marketing authorization. **(Grade C)**

Gait and Balance Impairment

- Physiotherapy interventions **(Grade B)** and the introduction of falls prevention programs, gait, core stability, and balance interventions **(Grade C)** as well as attentional training are recommended.
- Pharmaceutical management of chorea may improve walking and balance as they can be affected by chorea. **(Grade C)**
- The use of assistive devices such as four-wheeled walker as recommended by Physiotherapist or Occupational Therapist should be considered to improve stability and reduce fall risk. **(Grade B)**

Bruxism

- Injecting botulinum toxin A into the masseter muscles is proposed as the first-line treatment of bruxism. **(Grade C)**
- Customized protective mouth guards may be used to reduce the complications of bruxism on a case-by-case basis, mostly in early-stage patients.
- Bruxism may occur as a side effect of neuroleptics **(Grade C)** and serotonin reuptake inhibitors, thus reducing their dose should be considered.

Manual Dexterity

- Neuroleptics and tetrabenazine may possibly have a beneficial effect on dexterity as a result of reducing chorea. **(Grade C)**
- Management with physiotherapy and occupational therapy may be useful to reduce the functional impact of fine motor skill deterioration. **(Grade B)**

No pharmacological treatment is available for the management of cognitive disorders in HD.

Psychiatric Disorders

1. **Depression**
    - It is recommended to use a selective SSRI or a serotonin noradrenaline reuptake inhibitor (SNRI), or alternatively Mianserin or Mirtazapine, in case of sleep disruption. **(Grade B)**
    - In case of recurrent depression, long-term mood-stabilizer treatment may be introduced in complement to the treatment of the current episode to prevent relapses.
2. **Irritability**
    - Before initiating pharmacological treatment, possible environmental causes for the patient's frustration and irritability should be explored.
    - In order to reduce irritability, behavioral strategies should be considered.
    - Whilst SSRIs are first lines for irritability, it may be necessary to use them at or near the maximum recommended dose in order to be effective. **(Grade C)**
    - Irritable patients who do not benefit from an SSRI alone may benefit from combination therapy with Mianserin or Mirtazapine, especially when sleep disorders are present.
    - In patients with aggressive behavior, the recommended first-line treatment is a neuroleptic. **(Grade C)**
    - In case of overt aggression associated with depression, neuroleptic treatment should be associated with sedative antidepressants.
    - If irritability does not respond to antidepressant therapies and/or neuroleptics, a mood stabilizer can be added. **(Grade C)**
3. **Anxiety**
    - SSRI or SNRI are first line treatments for anxiety, especially when associated with depression.
    - Neuroleptics are valuable therapeutic alternatives in the treatment of anxiety when other treatments fail. **(Grade C)**
4. **Obsessions**
    - If pharmacological treatment is necessary for perseverative symptoms, an SSRI could be prescribed. **(Grade C)**
    - Olanzapine and risperidone are two valuable therapeutics for ideational perseverations, in particular when they are associated with irritability.

- If pharmacological treatment is necessary for obsessive-compulsive phenomena, a SSRI should be prescribed as first-line treatment. **(Grade C)**

5. **Sexual Impairment**
    - In case of impotence, prescription of phosphodiesterase 5 inhibitors should be considered.
    - If hypersexuality involves social discomfort or violence, the proposed first-line treatment is a neuroleptic and/or a SSRI. **(Grade C)**
    - If the treatment for hypersexuality with neuroleptics and/or SSRI is not successful, the addition of or substitution for an anti-androgen may be proposed. **(Grade C)**
6. **Hallucinations**
    - Second generation neuroleptics are the first line treatment for hallucinations and delusions. **(Grade C)**
    - Clozapine should be proposed as the first-line treatment in the case of akinetic forms of HD with debilitating Parkinsonian symptoms.
    - Perseverative ideation can sometimes mimic psychotic symptoms, and in such circumstances the patient may benefit from treatment with serotoninergic antidepressants in combination with an atypical neuroleptic.
    - If pharmacological treatments fail, the option of ECT can be discussed with psychiatrists. **(Grade C)**
7. **Agitation**
    - When agitation is associated with an anxiety disorder, a benzodiazepine should be prescribed as needed to reduce the risk of dependence and falls. **(Professional agreement)**
    - Some benzodiazepines (e.g., midazolam) may be useful in emergency situations. **(Grade C)**
    - Long-term treatment with benzodiazepines should be avoided as much as possible but remains necessary in some patients. **(Grade C)**
    - In the case of extreme agitation, and if there are associated behavioral and personality disorders, it is advised to prescribe a neuroleptic. **(Grade C)**
8. **Sleep Disorders**
    - Simple lifestyle and dietary strategies (e.g., avoiding long naps, having no stimulants after 4 pm) are the first-line treatment of insomnia.

- When lifestyle strategies are ineffective to treat insomnia, prescribing a hypnotic may be suggested for a short duration to avoid the risk of drug dependence.
- Some agents may be proposed in place of a hypnotic and for a long duration (e.g., mianserin, mirtazapine, and antihistaminic drugs) as they have a reduced tendency for causing dependency.
- Melatonin may be suggested in case of sleep phase inversion.
- A neuroleptic should be prescribed in the evening when sleep disorders are associated with behavioral disorders or chorea.

9. Urinary Incontinence

- Carbamazepine may be of benefit for diurnal unexpected complete urination. **(Grade C)**
- In the case of an overactive bladder with leakage and urge incontinence, therapy with selective antimuscarinic may be tried, whilst watching out for the appearance of potential side effects, in particular confusional state.
- If, after few weeks, the incontinence therapy has not been effective, it should be stopped.

10. Weight Loss

- When weight loss is observed, high-calorie and high-protein food supplements should be prescribed under instruction and monitored by a dietician/nutritionist. **(Grade C)**
- A Mediterranean diet may improve Quality of Life and nutritional composition. **(Grade C)**
- In case of the initiation of antidepressant and/or neuroleptic treatments, treatments inducing weight gain should be preferred in patients with significant weight loss, whilst treatments inducing weight loss should be avoided. **(Grade C)**

11. Hypersalivation

- In the absence of a specific treatment for HD, drugs used in other chronic diseases may be considered to reduce salivary secretion: scopolamine given percutaneously, atropine given orally or other drugs that have an anticholinergic effect (amitriptyline), whilst watching out for iatrogenic risks, in particular confusional state, constipation, ocular hypertension, and urinary retention.

- Injections of botulinum toxin into the salivary glands may be considered in a specialized setting if oral or oral mucosa treatment options have not induced benefit or were not well-tolerated.

1.2.2 Clinical Management of Neuropsychiatric Symptoms of Huntington Disease: Expert-Based Consensus Guidelines on Agitation, Anxiety, Apathy, Psychosis and Sleep Disorders [2018]

The following guidelines do not provide a specified grade of evidence or level of recommendation.

An international core committee joining forces between the European Huntington's Disease Network and the Huntington Study Group has issued guidelines on the management of neuropsychiatric symptoms of Huntington's Disease; the recommendations are detailed below[13]:

Management of Agitation in HD

- For acute agitation that is not responsive to behavioral strategies, the preferred pharmacologic options include use of either a benzodiazepine or an antipsychotic drug.
- For chronic agitation characterized by recurrent and ongoing distress, or continuing threat of harm to self or others pharmacologic options include either an antipsychotic or a mood-stabilizing antiepileptic drug.
- Consider a trial of pain medication when other therapies have failed for agitation in individuals who are unable to verbally communicate cause of distress.

Management of Anxiety in HD

- An SSRI drug is the preferred pharmacologic option for treatment of anxiety when it occurs either as an isolated symptom or when coexisting depression or obsessive perseverative behaviors are present.
- A warning should be given of potential short-term exacerbation of anxiety when an SSRI is initiated.

  If exacerbation occurs it may be appropriate to add a short-term course (one or two weeks) of a benzodiazepine.
- Alternative serotonergic drugs (SSRI, NSRI, clomipramine) are pharmacologic options if the initial SSRI is ineffective or not tolerated.
- Mirtazapine is a pharmacologic option particularly if coexisting sleep disorder is present.

- An antipsychotic is a pharmacologic option particularly if needed for treatment of coexisting chorea.
- Clomipramine is a pharmacologic option particularly if needed for coexisting obsessive perseverative behaviors.
- Long-term use of a benzodiazepine drug is discouraged in ambulatory individuals with HD unless all other options have failed.

1.3 North American Guidelines

1.3.1 Huntington's Disease Society of America: A Physician's Guide to the Management of Huntington's Disease – Third Edition [2011]

The following guidelines do not provide a specified grade of evidence or level of recommendation.

The Huntington's Disease Society of America (HDSA) published its third edition of the guidelines for the management of Huntington's Disease; the recommendations are detailed below[14]:

Diagnosis of HD:

- Traditionally, the clinical diagnosis of HD is based on the observation of involuntary movements in a patient with an appropriate family history, and supportive social history such as a decline in function or insidious onset of mood disturbance.
- The most accurate diagnostic confirmation of HD uses the direct genetic test, which counts the number of CAG repeats in the HTT gene using DNA obtained from a blood sample.
- Genetic testing is particularly useful when there is an unknown, or negative family history or when the family history is positive, but the symptoms are atypical.

Stages of HD:

Huntington's Disease can be divided into three stages: early-stage, middle stage, and late-stage HD.

- In early-stage HD, individuals are largely functional and may continue to work, drive, handle money, and live independently. Symptoms may include minor involuntary movements, subtle loss of coordination, difficulty thinking through complex problems, and perhaps some depression, irritability, or disinhibition.

- In middle stage HD, individuals lose the ability to work or drive and may no longer be able to manage their own finances or perform their own household chores, but will be able to eat, dress, and attend to personal hygiene with assistance. Chorea may be prominent, and people with HD have increasing difficulty with voluntary motor tasks. There may be problems with swallowing, balance, falls, and weight loss. Problem solving becomes more difficult because individuals cannot sequence, organize, or prioritize information.
- In late-stage HD, individuals require assistance in all activities of daily living. Although they are often nonverbal and bedridden in the end stages, it is important to note that people with HD seem to retain some comprehension. Chorea may be severe, but more often it is replaced by rigidity, dystonia, and bradykinesia. Psychiatric symptoms may occur at any point in the course of the disease but are harder to recognize and treat late in the disease due to communication difficulties.

The Total Functional Capacity (TFC) Rating Scale (table 3) is based on functional abilities that rates the patient's level of independence in five domains: occupation, ability to manage finances, ability to perform domestic chores, ability to perform personal activities of daily living, and setting for level of care.

Table 3. Total Functional Capacity Rating Scale

Domain	Ability	Score
Occupation	Unable	0
	Marginal work only	1
	Reduced capacity for usual job	2
	Normal	3
Finances	Unable	0
	Major assistance	1
	Slight assistance	2
	Normal	3
Domestic chores	Unable	0
	Impaired	1
	Normal	2
Activities of daily living	Total care	0
	Gross tasks only	1
	Minimal impairment	2
	Normal	3
Care level	Full-time nursing care	0

	Home for chronic care	1
	Home	2
Total	**Range 0-13**	

Clinicians use the TFC score to determine the disease stage according to the Shoulson and Fahn rating scale (table 4).

Table 4. Shoulson and Fahn Staging Scale

TFC Total Score	Stage
11-13	I
7-10	II
3-6	III
1-2	IV
0	V

Management of HD Associated Disorders

Although there is no cure for HD at present, current treatments, including physical therapy, occupational therapy, speech therapy, psychotherapy, and specific pharmaceuticals, can help manage the symptoms of the condition.

1. Chorea

In 2008, the FDA approved Tetrabenazine for the treatment of chorea in Huntington's Disease.

- The initial dose of Tetrabenazine is 12.5 mg daily; it may be increased weekly by 12.5 mg in 2-3 divided doses per day up to 50 mg/day.
- For milder chorea, a dose of 12.5 mg twice daily may be effective, with higher doses reserved for more severe chorea.
- The dose of Tetrabenazine should be halved for people with HD who are also taking strong CYP2D6 inhibitors.
- The FDA recommends CYP2D6 genotyping for individuals who require a dose of > 50 mg/day to identify fast- and slow-metabolizers.

Individuals who do not tolerate tetrabenazine, or have other contraindications to its use, may benefit from off-label use of neuroleptics for reduction in chorea.

Typical neuroleptics such as haloperidol or fluphenazine are quite effective. Some atypical neuroleptics such as olanzapine and risperidone may also be effective. Some atypical neuroleptics as quetiapine and clozapine are ineffective for chorea.

The following table depicts the agents used as anti-chorea therapy:

Table 5. Pharmacological Treatment Regimens for Chorea

Medication	Initial dose	Maximal dose	Side effects
Tetrabenazine	12.5 mg	50 mg/day	Depression, akathisia, worsening of voluntary motor control Sedation
Haloperidol	0.5-1 mg	10-15 mg/day	Extrapyramidal syndrome (abnormal involuntary movements): akathisia, dystonia, bradykinesia Sedation
Fluphenazine	1-2 mg	10 mg/day	Extrapyramidal syndrome Sedation
Risperidone	0.5-1 mg	5-10 mg/day	Extrapyramidal syndrome at higher doses Sedation
Olanzapine	1.25-2.5 mg	10-15 mg/day	Extrapyramidal syndrome Sedation Weight gain and metabolic syndrome

2. **Dystonia**

Treatment approaches may include benzodiazepines, baclofen, and dopaminergic agents developed for Parkinson's disease.

- For focal dystonia, Botulinum toxin injections performed by a trained professional. may be effective.
- For severe dystonia, patients may benefit from braces, pads, or splints for affected joints; a physical or occupational therapist can assist in the evaluation and dispensing of appropriate equipment.

3. **Bradykinesia**

Anti-chorea therapy may unmask or worsen bradykinesia. If this impacts the functional capacity of the patient, a reduction in dosage or the withdrawal of neuroleptics and/or tetrabenazine should be considered.

Bradykinesia in people with juvenile onset HD, and adults with the rigid/dystonic form of HD, may improve with treatment using carbidopa/levodopa.

4. **Tics**

If severe, tics may be reduced by using benzodiazepines, SSRIs, neuroleptics and possibly by off-label use of tetrabenazine.

5. **Myoclonus**

Myoclonus and tremor are much more commonly seen in juvenile onset HD or in young adults. Clonazepam is deemed an effective agent for the management of Myoclonus.

6. **Rigidity**

Rigidity may occur early in juvenile or adult akinetic/rigid HD, but is also common in advanced HD.

Rigidity may be improved by reduction or cessation of tetrabenazine or neuroleptic drugs, or by adding dopaminergic drugs.

7. **Impaired Voluntary Motor Control**

Progressive loss of voluntary motor control is a core feature of HD.

This symptom starts early in the disease, progresses inexorably, and correlates with disability.

a. **Gait Impairment and Falls**

Gait impairment and falls typically occur in mid to late-stage HD.

Early referral to a physical therapist for gait assessment, balance and postural exercises is strongly recommended.

As gait difficulties increase, the use of proper footwear and adaptive equipment should be encouraged.

The equipment includes wheelchairs with handbrakes or other assistive devices such as canes or walkers.

b. **Speech Impairment**

With disease progression, speech becomes slower, and the voice may become hypophonic or explosive. Referral to a speech-language pathologist may be indicated when articulation or intelligibility is affected.

c. Swallow Dysfunction and Choking

The automatic coordination of bringing food to the mouth, chewing, forming a bolus, and swallowing, while simultaneously inhibiting breathing is hindered in patients with HD. Poor coordination may lead to frequent choking on liquids and on solid food. Aspiration of liquids or food may lead to pneumonia or even to death by choking.

A speech-language pathologist should assess the individual with dysphagia periodically and suggest adaptations that will improve swallowing and minimize choking.

Eating slowly, avoiding distractions during mealtimes, adjusting food textures, and using adaptive equipment are all helpful in reducing choking.

Nutritional needs can be met by liquid supplements alone for some individuals.

Gastrostomy tubes placed by percutaneous endoscopy or interventional radiology can provide palliation of suffering and afford maintenance of hydration and nutrition in late-stage disease.

d. Incontinence

Bladder and bowel incontinence may occur in mid to late-stage HD. People with HD also frequently suffer from urinary tract infections due to incomplete emptying of the bladder. Setting up a regular schedule for toileting is often helpful.

If problems persist or are severe, referral to a urologist or urogynecologist is strongly recommended, as both pharmacologic and behavioral techniques can help significantly.

e. Seizures

Seizures are more likely to occur in younger adults with HD. Careful history and medical work-up is indicated, together with brain imaging and electroencephalogram (EEG).

If unprovoked seizures are suspected, pharmacologic treatment should be instituted based on the seizure type and concomitant medications.

f. Weight Loss

Weight loss is common in moderate to late-stage HD.

Referral to a speech-language pathologist is recommended for a formal swallowing evaluation, once feeding or swallowing difficulties arise. The speech-language pathologist can instruct people with HD and caregivers in techniques to reduce choking, such as changing food textures.

A dietitian or nutritionist may be helpful in developing high calorie dietary plans that promote maintenance of weight and nourishment. If dysphagia is severe, high-protein liquid food supplements should be offered.

8. Psychiatric Disorders

a. Depression

There is no single preferred antidepressant for treating depression in HD.

HD patients are sensitive to the cognitive side effects of some antidepressants; they are mainly prone to develop delirium.

Older agents such as tricyclic antidepressants (TCAs) and monoamine oxidase (MAO) inhibitors should generally be **avoided**.

The use of selective serotonin reuptake inhibitors (SSRI), such as fluoxetine, sertraline, paroxetine, citalopram, or escitalopram is **recommended** for reasons of safety and tolerability.

If the patient's depression is accompanied by delusions, hallucinations, or significant agitation, it may be necessary to **add an antipsychotic** medication to the regimen, preferably in **low doses** to minimize the risk of sedation, rigidity, or parkinsonism.

If the neuroleptic is being used for a purely psychiatric purpose, and not for suppression of chorea, the physician may want to prescribe one of the newer agents such as risperidone, olanzapine, quetiapine, ziprasidone, or aripiprazole.

Older neuroleptics such as haloperidol or fluphenazine tend to be less sedating, but cause more parkinsonism, which is why they have often been used in small doses to suppress chorea.

Benzodiazepines, particularly short acting drugs such as lorazepam, may be another good choice for the short-term management of agitation.

Neuroleptics and benzodiazepines used for the management of acute agitation should be tapered as soon as possible.

Electroconvulsive therapy (ECT) has also been found to be effective in HD patients with depression. This treatment should be considered if a person does not respond to several good trials of medication, or if a more immediate intervention is needed for reasons of safety.

b. Mania

Therapy beginning with divalproex sodium at a low dose such as 125 to 250 mg po bid and gradually increasing to efficacy, or to reach a blood level of 50-150 mcg/ml is recommended.

Several other anticonvulsants are sometimes used for treatment of mania, including lamotrigine, topiramate, and carbamazepine.

Manic people with HD, particularly those who are very agitated or who have delusions and hallucinations, may require a neuroleptic, or possibly a benzodiazepine for immediate control of these symptoms.

In cases of extreme agitation, a rapidly acting injectable agent may be necessary.

c. Apathy

Non-sedating antidepressants such as SSRIs or Bupropion are suggested to be helpful in patients with apathy even if they do not meet the criteria for depression.

Individuals with primary apathy sometimes respond to psychostimulants such as methylphenidate, pemoline or dextroamphetamine.

Anecdotal reports have been published regarding the successful treatment of apathy with amantadine, bromocriptine, and selegiline.

Apathy can be worsened by medications known to blunt emotion or slow cognitive processing, such as neuroleptics or benzodiazepines.

d. Perseveration or Fixation

Treatment with SSRIs is proposed for their possible anti-obsessive effect. There exists a theoretical basis for a dopamine-augmenting strategy in the treatment of executive dysfunction.

There have been several cases of successful treatment with amantadine.

e. Irritability

HD patients may respond to antidepressants, particularly SSRIs (sertraline, fluoxetine, and paroxetine).

In severe or urgent situations most clinicians would probably start with a neuroleptic, particularly one of the newer agents which tend to have fewer side effects. Long-acting benzodiazepines, such as clonazepam, starting at low doses, e.g., 0.5 mg/day, have also been helpful.

Mood stabilizers, such as divalproex sodium and other anticonvulsants, have also been helpful and could be administered as outlined for mania.

f. Delirium

Low doses of neuroleptics may be helpful in managing the agitation of a delirious individual temporarily.

g. Anxiety

Common agents for anxiety include SSRIs, benzodiazepines, and non-benzodiazepine anxiolytics such as Buspirone.

h. Panic Disorder

The usual treatment consists of SSRIs, sometimes temporarily supplemented with benzodiazepines. SSRIs are usually mildly stimulating and should be initiated at the **lowest** dose.

Benzodiazepines should be used judiciously because of the vulnerability of HD patients to delirium and falls, and because of their potential for abuse, especially in those whose judgment may already be impaired.

Some HD patients will respond to the non-benzodiazepine anxiolytic buspirone, which can be started at 5 mg two to three times per day and advanced to 20-30 mg per day in divided doses.

i. Sexual Impairment

Although not well established in HD specific cases, anti-androgenic therapy has been found to be helpful in a few cases of sexual impairment.

j. Sleep Problems

Agents such as sedating antidepressants (such as trazodone) or neuroleptics (such as quetiapine) may be used judiciously.

Benzodiazepines and other prescription sedative-hypnotics are potentially delirogenic and habit forming and should be used cautiously, if at all.

Juvenile Onset Huntington's Disease (JHD)

Typical initial symptoms of juvenile onset HD: positive family history of HD (usually in the father), stiffness of the legs, clumsiness of arms and legs, decline in cognitive function, changes in behavior, seizures, changes in oral motor function, chorea in an adolescent and behavioral disturbances.

Staging is based on several factors (table 6).

Table 6. Stages of Juvenile Onset Huntington's Disease

Stage of JHD	Total Points in All Areas	
1	11-13	
2	7-10	
3	3-6	
4	1-2	
5	0	
Area	**Points**	**Description**

School attendance	3	attends school, no special assistance needed
	2	attends school, some regular classes, some special or modified classes
	1	attends school, few, or no regular classes
	0	unable to attend school or work program
Academic/ developmental performance	3	reading/writing/math skills appropriate to age
	2	mild decrease in academic performance but still able to take a test or to write
	1	unable to write legibly but able to communicate orally
	0	unable to read/write/communicate orally
Chores	2	able to assist in age-appropriate manner with household chores
	1	occasionally assists with chores
	0	unable to participate in household chores
Activities of daily living	3	performs self-cares in an age-appropriate manner
	2	requires some assistance for bathing, dressing, grooming, or feeding
	1	assists others who bathe, dress, or feed him/her
	0	unable to assist in self-cares
Lives	2	at home with only family assistance
	1	at home/group home/foster care with assistance from non-family members
	0	living in a long-term care facility

Treatments and therapies for the movement disorder: no medications improve control of voluntary movements, although there are treatments for rigidity, spasticity, dystonia, and chorea that may help children with JHD as mentioned above.

Treatments and therapies for cognitive disorders: No medications have been proven to improve cognitive function in HD.

If frequent seizures, attention deficit, or depression are interfering with a child's ability to perform, treating these symptoms may improve the child's quality of life.

The management of psychiatric disturbances are detailed based on recommendations from "The Juvenile HD Handbook"[15]:

1. **Management of Depression**

SSRIs are the most used in recent years, because of their favorable side effect profile. No antidepressant is specifically preferred over others in HD patients.

The following antidepressants are frequently used in practice: Tricyclic antidepressants (Amitriptyline, Nortriptyline, Imipramine, Clomipramine), Selective serotonin reuptake inhibitors (Fluoxetine, Sertraline, Citalopram, Escitalopram, Paroxetine), Serotonin-norepinephrine reuptake inhibitors (Venlafaxine, Bupropion) and other agents include Trazodone and Mirtazapine.

2. **Management of Aggressive, Explosive or Violent Behavior**

Potential agents that may be used include mood stabilizers such as valproic acid and lamotrigine, antipsychotic agents such as haloperidol, olanzapine, or risperidone, sedatives such as lorazepam or clonazepam, or beta-adrenergic blockers such as propranolol.

Some children may have attention deficit disorder or hyperactivity in addition to HD; For these children, treating these symptoms may lead to an improvement in behavior.

3. **Obsession**

Behavioral modification strategies may be opted for the management of obsession.

Medications such as SSRIs or clomipramine can be used to suppress obsessive thoughts.

4. **Hallucinations**

The mainstay of treatment for hallucinations and for delirium are the antipsychotic or neuroleptic drugs.

Older antipsychotic drugs include haloperidol, thorazine, and fluphenazine, among many others.

A newer group of "selective" antipsychotics, designed to have fewer side effects, includes risperidone, olanzapine, clozapine, and quetiapine, among others.

5. **Seizures**

Children with HD who have seizures usually have generalized or myoclonic epilepsy, although other seizure types are possible (focal or partial complex seizures).

Valproic acid and lamotrigine are considered first choices for the treatment of myoclonic epilepsy.

A wide range of anticonvulsant drugs are available to treat generalized seizures or partial complex seizures; none is specifically recommended or avoided because the child has HD.

Phenytoin, carbamazepine, levetiracetam, topiramate, and zonisamide are among the favored drugs; the selection of a medication should be made carefully after the evaluation is completed.

Management of Late-Stage Huntington's Disease

Late-stage HD can be characterized by the need for 24-hour supervision and care.

Table 7 includes possible management strategies for different manifestations of movement disorders in late-stage HD.

Table 7. Management of Movement Disorders in Late-Stage HD

Symptom	Functional Result	Team Members	Possible Management Strategy
Chorea	Bruising, abrasions; falling out of chair or bed; restraints	Medical doctor (MD), occupational therapist (OT), nursing, maintenance department	Medications, padding of environment or body, special seats, floor mattress, avoid limb and trunk restraints; remove long cords (such as nurse call lights); frequent monitoring for bruises, skin tears, other injuries
Incoordination of hands, arms	Inability to perform activities of daily living (ADLs)	OT, nursing	Assistance with ADLs, modified equipment for eating; OT training to optimize function
Gait disturbance	Falls, reduced mobility	Physical therapist (PT), OT	Monitor and document falls; pad environment or body, acclimate early to wheelchair; (occasional

			person can use Merry Walker or walker); family communication
Ballistic movements	Falls, limb injury, breaking furniture and toilet	OT, maintenance department	May need Broda or Q foam chair, concrete toilet, other special equipment; low bed or floor mattress
Dystonia	Contractures, impaired oral or perineal hygiene, skin breakdown; inability to eat	Nursing, OT, physician	Botox injections, oral medications, skin care plan, gastrostomy tube

Table 8 includes management strategies for oral-motor dysfunction:

Table 8. Management of Oral-Motor Dysfunction in Late-Stage HD

Symptom	Functional Result	Team Members	Possible Management Strategy
Oral motor dysfunction	Dysphagia, drooling, choking, aspiration; weight loss	Speech language pathologist (SLP), nursing, physician, dietitian	Medications/Botox for drooling, change food textures, train in safe feeding strategies; increase calorie intake (high calorie supplements); gastrostomy tube; 24-hour access to food
Speech dysfunction	Reduced communication skills; mutism	SLP, nursing	Simple word board, computer-based assistive communication device, thoughtful care from staff/ family who know person well

Table 9 includes management strategies for behavioral and psychological manifestations:

Table 9. Management of Behavioral Issues in Late-Stage HD

Symptom	Functional Result	Possible Management Strategy
Depression	Withdrawal, sadness, suicidality	Medications, counseling, spiritual support, family involvement, suicide risk assessment and documentation
Anxiety	Behavioral over activity, nervousness, substance abuse	Medications, counseling, distracting activities, care plans about cigarette, drug, alcohol use
Paranoia/ Suspiciousness	Resisting care, fights with other residents, overt hallucinations	Change rooms or roommates, behavioral modification, care plans around hygiene, medications (consider IM depot or oral-dissolving preparations)
Irritability	Resistiveness with staff and other residents	Medications, rule out depression, spiritual support, family involvement, environmental strategies
Impulsiveness	Dangerous behaviors, aggressive behaviors	Medications, wander guard or seat/bed alarm, other environmental strategies
Obsessiveness/ Perseveration	Stickiness (disturbing staff and other residents); smoking	Engage in activities, behavioral modification; smoking cessation using nicotine patches, inhalers, other medications
Explosive/ Aggressive/ violent behavior	Danger to staff and other residents	Care plan for each behavior, identify triggers, know when to call for emergency help, possible prn medications, change roommates or room, engage in other activities
Screaming	Disruptive loud behavior	Evaluate for pain, depression; consider hospice care

Sexually inappropriate behavior	Danger to self or other residents	Careful documentation of behavior, protection of at-risk individuals, environmental changes, pregnancy and STD prevention, rarely medication to reduce libido
Somatic delusions	Non-organic “pain”, eating disorder, obsession with bowels, sensation of “skin crawling”	Involvement in distracting activities, psychiatric evaluation, medications

1.3.2 American Academy of Neurology Evidence-Based Guideline: Pharmacologic Treatment of Chorea in Huntington Disease [2012]

The American Academy of Neurology has issued guidelines for the management of Chorea associated with HD; it has opted for the following grades of recommendation/level of evidence:

Table 10. AAN Grade of Recommendation/Level of Evidence

Level of Obligation	Definition
A	Established as effective, ineffective, or harmful (or established as useful/predictive or not useful/predictive) for the given condition in the specified population. (Level A rating requires at least two consistent Class I studies.)
B	Probably effective, ineffective, or harmful (or probably useful/predictive or not useful/predictive) for the given condition in the specified population. (Level B rating requires at least one Class I study or two consistent Class II studies.)
C	Possibly effective, ineffective, or harmful (or possibly useful/predictive or not useful/predictive) for the given condition in the specified population. (Level C rating requires at least one Class II study or two consistent Class III studies.)
U	Data inadequate or conflicting; given current knowledge, treatment (test, predictor) is unproven.

The recommendations are detailed below[16]:

- If HD chorea requires treatment, clinicians should prescribe TBZ (up to 100 mg/day), amantadine (300 – 400 mg/day), or Riluzole (200 mg/ day) (Level B).
- TBZ likely has very important antichoreic benefits, and Riluzole 200 mg/day likely has moderate benefits (Level B).
- The degree of benefit for amantadine is unknown. Clinicians should discuss possible AEs with patients with HD and monitor for their occurrence, particularly parkinsonism and depression/suicidality with TBZ and elevated liver enzymes with Riluzole.
- Clinicians may prescribe nabilone for modest decreases in HD chorea (Level C), but information is insufficient to recommend long-term use, particularly given abuse potential concerns (Level U).
- Riluzole 200 mg/day likely decreases chorea. Clinicians should not prescribe Riluzole 100 mg/day for moderate short-term benefits (Level B) or for any long-term (3-year) HD antichoreic goals (Level B).
- Clinicians may choose not to prescribe ethyl-EPA (Level B), minocycline (Level B), or creatine (Level C) for very important improvements in HD chorea.
- Clinicians may choose not to prescribe coenzyme Q10 (Level B) for moderate improvements in HD chorea.
- Data is insufficient to make recommendations regarding use of clozapine, other neuroleptics, or donepezil for HD chorea treatment (Level U).

1.4 European Guidelines

1.4.1 Guidelines for Clinical Pharmacological Practices in Huntington's Disease [2016]

The French National Huntington Disease Reference Centre and the reference center for neurogenetic diseases formed a committee that issued guidelines for the management of Huntington's Disease; the committee has opted for the following grading of the guidelines[17]:

Table 11. Grading of Recommendations/Level of Evidence

Level of Published Scientific Evidence	Grade
Level 1 Randomized controlled trials (RCTs) of high power Meta-analyses of RCTs	A: Established scientific evidence

Level 2 RCTs of low power Properly conducted non-RCTs Cohort studies	B: Presumed scientific foundation
Level 3 Case-control studies	
Level 4 Comparative studies with major biases Retrospective studies Case series Epidemiological descriptive studies	C: Low level of evidence

The recommendations are detailed below:

<u>Treatment of Motor Dysfunction</u>

1. **Chorea**
    - **Tetrabenazine** is beneficial for the treatment of chorea. **(Grade A)**
    - Riluzole is not deemed beneficial for the treatment of chorea. **(Grade A)**
    - **Second-generation antipsychotics** are the first-choice treatment when the patient has suffered, in addition to chorea, from changes in character, behavior, or psychotic or ongoing depressive illness. **(Grade C)**
    - The use of amantadine is not recommended, based on its conflicting results in clinical trials. **(Expert agreement)**
    - An abrupt increase of chorea should prompt a search for, and treatment of, an intercurrent disorder (anxiety, digestive disease, infection, pain, etc.) before considering strengthening the anti-chorea treatment. **(Expert agreement)**
    - Appropriate protective measures (for beds, chairs, tables, patient transfers, washing, etc.) should be put in place if chorea is severe and likely to lead to traumatic injury.

2. **Dystonia**
    - In cases of focal dystonia, botulinum toxin may be indicated. **(Expert agreement)**
    - Benzodiazepines, particularly clonazepam, may be suggested if healthcare professionals (HCPs) are on the lookout for any potential adverse effects and risk of drug dependence. **(Expert agreement)**

3. **Akinesia and Rigidity**
    - Levodopa can provide partial and temporary relief of akinetic–rigid symptoms of HD. **(Grade C)**
    - Dopamine agonists and amantadine can also be helpful, especially in cases of failure with levodopa for akinetic–rigid forms. **(Grade C)**
    - Both levodopa and dopaminergic agonists should be started gradually, without the use of high doses, to limit adverse events and psychiatric effects (800 mg of levodopa is usually the maximum dose, given the absence of obvious benefit with higher doses). **(Grade C)**

4. **Swallowing Disorders**
    - The management of swallowing disorders in HD is based on clinical evaluation and swallowing assessment by expert opinion, and should involve advice on posture and installation, appropriate food texture, rehabilitation of facial oral praxis, pneumophonic coordination and the elimination of distraction factors. **(Grade C)**
    - No pharmacological treatment has proved effective for these disorders.
    - In advanced disease, percutaneous endoscopic gastrostomy feeding may be considered on a case-by-case basis.

5. **Myoclonus**
    - When myoclonus is associated with seizure, treatment with sodium valproate or clonazepam, either alone or in combination, with escalating doses is recommended. **(Grade C)**
    - If myoclonus is not associated with seizures, then Piracetam is a licensed treatment, although the useful dose is > 12 g/day. Levetiracetam is a therapeutic alternative. **(Expert agreement).**

6. **Impaired Gait and Balance**
    - Pharmacological treatments for reducing chorea (Tetrabenazine, antipsychotics) can also improve gait and balance. **(Grade C)**
    - Management of gait and balance, and prevention of their main complications (falls, loss of autonomy), are based on rehabilitative measures (physiotherapy, psychomotor therapy).
    - Prescription of the appropriate technical aids (rollators or rolling walkers, canes, wheelchairs) and/or protective clothing (helmets, kneepads, elbow, and wrist guards) should also be considered to reduce the complications of falls.

7. **Bruxism**
    - Injection of botulinum toxin A into the masseter muscles is proposed as the first choice of treatment and may be renewed every 3 to 6 months in cases of bruxism recurrence. **(Grade C)**

8. **Manual Dexterity**
    - Whereas no treatment specifically targets manual dexterity, the second-generation antipsychotics and tetrabenazine can improve dexterity by reducing chorea. **(Grade C)**

<u>Treatment of Psychiatric Manifestations</u>

1. **Depression**
    - Depression should be treated by antidepressants whenever it arises in HD, particularly selective serotonin reuptake inhibitors (SSRIs) or serotonin–norepinephrine reuptake inhibitors (SNRIs), or mianserin if a sleep disorder is present.
    - In cases of recurrent depression, emotional lability, impulsivity and irritability, the introduction of a mood stabilizer may be helpful.

2. **Irritability & Aggression**
    - In patients with predominantly aggressive behaviors, or significant impulsive or psychotic symptoms, second-generation antipsychotics (olanzapine or risperidone) are recommended as first-line treatment. **(Grade C)**
    - If irritability is related to depression, then an SSRI is recommended. **(Grade C)**
    - If the antidepressant treatment is effective for the depression, but the irritability persists, then an antipsychotic (preferably second-generation) or mood stabilizer, such as valproic acid, valpromide, carbamazepine, lamotrigine, or lithium, should also be prescribed. **(Grade C)**
    - For non-compliant patients, long-acting injectable antipsychotics should be used. **(Grade C)**

3. **Apathy**
    - Second-generation antipsychotics (olanzapine) are especially of interest when anxiety is associated with ideational perseveration, or personality or behavior disorders. **(Grade C)**
    - An SSRI or SNRI is also recommended, particularly if there is associated depression. **(Expert agreement)**

- Prompt prescription of an anxiolytic (benzodiazepine, buspirone) or cyamemazine may also be useful. **(Expert agreement)**

4. **Sexual Disorders**
    - In cases of hypersexuality leading to discomfort, an antipsychotic can be used as a first-line treatment, especially if the sexual problems are part of a broader array of behavioral issues. **(Grade C)**
    - In cases of failure with an antipsychotic, the addition of, or replacement by, an antiandrogen may be suggested. **(Expert agreement)**
    - A lowered libido should trigger a search for an iatrogenic cause (SSRI use), in which case, a dose reduction or replacement of the offending treatment may be proposed. **(Expert agreement)**
    - In cases of erectile dysfunction, impotence treatment may be used. **(Expert agreement)**

5. **Obsessive Compulsive Disorder (OCD)**
    - SSRIs are the first line agents for the management of OCD. **(Grade C)**
    - In cases of failure, SSRIs may be replaced by a second-generation antipsychotic (olanzapine or risperidone). **(Grade C)**

6. **Hallucinations**
    - Second generation antipsychotics; particularly olanzapine or risperidone, are recommended for the management of hallucinations. **(Grade C)**
    - In cases of a lack of efficacy of these antipsychotics, a first-generation antipsychotic may be proposed. **(Expert agreement)**
    - Clozapine may be suggested as the second-line drug in cases of resistance to first-line treatments but is also a first-line agent in cases of akinetic forms with disabling parkinsonism. **(Expert agreement)**
    - For non-compliant patients, injectable sustained-release antipsychotics are an alternative. **(Expert agreement)**

7. **Agitation**
    - Severe agitation may require antipsychotics, especially second-generation with injection delivery, if behavior and personality disorders are associated. **(Grade C)**
    - If agitation is associated with an anxiety disorder, a benzodiazepine should occasionally be prescribed. **(Expert agreement)**

No treatment has been proven effective in the pharmacological treatment of **cognitive disorders**.

Treatment of Somatic/Autonomic Impairment

1. Sleep Disorders

- Lifestyle changes and dietary rules, such as taking short naps, removing stimulants after mid-afternoon, and waking up at a fixed time, are recommended as the first line of treatment.
- When these are ineffective, hypnotic drugs may be proposed, but at the lowest doses and for the shortest period to avoid dependence.
- If behavioral disorders or chorea are associated, then antipsychotic drugs should be taken in the evening.
- In some patients, supplementing with melatonin may be useful.

2. Urinary Incontinence

- Carbamazepine at 200 mg may be effective for unannounced diurnal urination (sudden and complete urination without prodrome), with or without nocturnal urinary incontinence. **(Grade C)**
- Antimuscarinic treatment may be offered in cases of proven overactive bladder with urge incontinence leaks. The more selective antimuscarinics (trospium, solifenacin) should be preferred to less selective (oxybutynin) ones, with monitoring for potential side-effects such as confusion. **(Grade C)**

3. Weight Loss

- Before weight loss happens, it is recommended to prescribe high-calorie and high-protein food supplements.
- Assessment by a dietitian is often helpful to ensure the amount and variety of nutrients provided, while considering the patient's eating habits and tastes to stimulate appetite.
- If antidepressant and/or antipsychotic treatments are indicated, a drug that induces weight gain should be preferred, while treatment that emphasizes weight loss should be avoided.
- Percutaneous gastrostomy may also be proposed on a case-by-case basis.

4. Hypersalivation

- Given the lack of specific treatment for HD, the drugs used for other chronic diseases may be considered for reducing salivary secretion, including

percutaneous scopolamine, oral atropine, or other drugs with anticholinergic effects (amitriptyline), but with caution, given the iatrogenic risk especially of agitation, constipation, and urinary retention.

- If oral or cutaneous treatment options have proved ineffective or have induced side-effects, then botulinum toxin injected into the salivary glands may be considered in certain specific settings.

Table 12. Summary of Huntington's Disease Clinical Features and Recommended Symptomatic Drugs

Domain	Symptom	Frequency	Evolution	Treatment	Grade
Motor	Chorea	+++	D > S and I	Tetrabenazine SGAP	A C
	Dystonia	+++	D	Botulinum Toxin Benzodiazepines	PA
	Falls	+++	D	-	-
	Choking	+++	D	-	-
	Dysphagia	++	D	-	
	Rigidity	++	D	Levodopa Dopamine agonists Amantadine	C
	Bradykinesia	+++	D	-	
	Myoclonus	+ mostly Juvenile HD	D or S	Sodium Valproate Clonazepam Piracetam Levetiracetam	C PA
	Dysarthria	+++	D	-	
	Motor impersistence	+++	D	-	
	Bruxism	+	D	Botulinum Toxin A	C
	Poor manual dexterity	+++		-	-
Psychiatric/ behavioral	Depression	+++	U	Antidepressant Mood stabilizer	C PA

	Apathy	+++	D	-	-
	Irritability/ aggression	+++	U	SGAP SSRI Mood stabilizer	C
	Obsessions, perseverations	++	D	SSRI SGAP	C
	Anxiety	+++	U	SGAP SSRI/SNRI	C PA
	Agitation	++	U	-	-
	Hallucinations/ delusions/ paranoia	+	U	SGAP	C
	Impatience	++	D,V	-	-
	Impulsivity	+++	D	-	-
	Suicidal ideation or attempts	++	U	-	-
	Sexual disorders	++	U	Antiandrogen Antipsychotics Impotence Treatment	C PA
Cognitive	Memory loss	+++	D	-	-
	Loss of fluency/ speech	+++	D	-	-
	Executive function/ attention	+++	D	-	-
	Social cognition impairment	+++	D,V	-	-
	Disorientation	+	D	-	-
	Bradyphrenia	+++	D	-	-
	Visuospatial & visual perceptual disorders	++	D	-	-

Somatic/ autonomic	Weight loss	+++	D,V	Food Supplements	PA
	Incontinence	+++	D	Carbamazepine Antimuscarinics	C PA
	Sleep disorders	++	U	Hypnotic drugs Melatonin	PA
	Gastrointestinal disorders	++	U	-	-
	Sweating	++	U	-	-
	Hypersalivation	++	D,V	Scopolamine Atropine Amitriptyline Botulinum toxin	PA
	Pain	+	U	Analgesics	PA
	Dental pain	++	-	-	-
For symptoms with no drug recommendations (e.g.**,** cognitive impairment), non-pharmacological interventions should be considered; +++: frequent, ++: common, +: uncommon; V: variable; U: unpredictable; D: progressive deterioration; I: improvement; S: stability; SGAP: second-generation antipsychotics; PA: professional agreement; SSRI: selective serotonin reuptake inhibitor; SNRI: serotonin–norepinephrine reuptake inhibitor.					

1.5 Systematic Reviews & Meta-Analyses

The table below tackles a systematic review and meta-analyses issued in **2023, 2021 and 2019** respectively for Huntington's Disease.

Table 13. Systemic Reviews and Meta-Analyses

Study	Author (year)	Study Title	Primary Objective	Outcomes	Results
1	Clark et al. (2023)[18]	*"A systematic review and meta-analysis of depression and apathy frequency*	Exploring depression and apathy frequency within individuals from families affected by	Depression frequency in the lifetime in adults affected by or at-risk for HD Apathy frequency in	Depression frequency in the lifetime in adults affected by or at-risk for HD was 38%, I^2 = 99%. Apathy frequency in the lifetime in adults affected by or at-risk for HD was 40%, I^2 = 96%. The robustness of the findings improved when limiting the analysis to gene-

		in adult-onset Huntington's disease"	HD, and within individuals with confirmed HD gene-positive status.	the lifetime in adults affected by or at-risk for HD	positive individuals only where apathy was found to be slightly more common than depression, 48% and 43% respectively.
2	Chen et al. (2021)[19]	*"Pridopidine for the Improvement of Motor Function in Patients with Huntington's Disease: A Systematic Review and Meta-Analysis of Randomized Controlled Trials"*	Evaluating the efficacy and safety of pridopidine in HD.	Unified Huntington's Disease Rating Scale (UHDRS)-modified Motor Score (mMS) UHDRS-Total Motor Score (TMS) Adverse Events	Pridopidine improved mMS and had no statistical significance in association with TMS or adverse events. Pridopidine (≥90 mg/day) improved TMS and mMS but increased adverse events, such as nasopharyngitis and insomnia. More RCTs were expected to assess pridopidine in HD.
3	Morsy et al. (2019)	*"Efficacy of ethyl-EPA as a treatment for Huntington disease: A systematic review and meta-analysis"*	After MRI studies suggested the efficacy of ethyl-EPA in reducing the progressive brain atrophy in Huntington disease, trials were conducted to test its efficacy as a treatment for Huntington disease.	Unified HD rating scale (UHDRS) or any scale used to assess the disease MRI results before and after the treatment of the patients Side effects and complications of ethyl-EPA	Meta-analysis results indicated that ethyl-eicosapentaenoic acid has no significant effect on any scale of HD at six months. At 12 months, two studies suggested significant improvements of the total motor score and total motor score -4 in both fixed and quality effect model [MD = -2.720, 95% CI (-4.76; -.68), P = 0.009], [MD = -2.225, 95% CI (-3.842; -0.607), P = 0.007] respectively. Maximal chorea score showed significant results [MD = -1.013, 95% CI (-1.793; -0.233), P = 0.011] in only fixed effect model, while no improvement was detected for Stroop color naming test or symbol digit modality.

Section 2.0 Drug Therapy

2.1 New Drugs

There are no SFDA registered drugs for the management of Huntington's Disease. The document mainly tackles supportive care and management of HD comorbidities that are discussed in detail in their respective CHI guidelines.

2.2 Other Drugs

2.2.1 Tetrabenazine

Tetrabenazine was initially approved by the FDA in 2008. It is used in the treatment of chorea associated with Huntington disease. Tetrabenazine is to be given as 12.5 mg once daily in the morning with a maximum single dose of 25mg. It is important to note that Tetrabenazine has a Black Box Warning for depression and suicidality whereby Tetrabenazine can increase the risk of depression and suicidal thoughts and behavior in patients with Huntington disease. Tetrabenazine has received a positive recommendation from HTA bodies as HAS[20].

2.2.2 Deutetrabenazine

Deutetrabenazine was initially approved by the FDA in 2017. It is used in the treatment of chorea associated with Huntington disease. Immediate release tablets are given as 6 mg twice daily with a maximum recommended dose of 48 mg/day. Extended-release tablets are given as 12 mg once daily with a maximum recommended dose of 48 mg/day. It is important to note that Deutetrabenazine has a Black Box Warning for depression and suicidality whereby Deutetrabenazine can increase the risk of depression and suicidal thoughts and behavior in patients with Huntington disease. Deutetrabenazine has received a negative recommendation from PBAC[21] attributed to the lack of clinical evidence.

2.2.3 Valbenazine

Valbenazine was initially approved by the FDA in 2017 for the treatment of tardive dyskinesia. It was then approved in August of 2023 for the management of chorea associated with Huntington's Disease. Valbenazine is used in the treatment of adults with chorea associated with Huntington disease. It is given as 40 mg once daily; the dose may be increased in 20 mg increments every 2 weeks to a target dose of 80 mg once daily. It is important to note that Valbenazine has a Black Box Warning for depression and suicidality whereby Valbenazine can increase the risk of depression and suicidal thoughts and behavior in patients with Huntington disease. No statements were issued from the concerned HTA bodies regarding its cost

effectiveness. The landmark trial for Valbenazine use in HD is titled **KINECT-HD**. This Phase 3, randomized, double-blind, placebo-controlled trial showed that valbenazine resulted in improvement in chorea compared with placebo and was well tolerated. Continued research is needed to confirm the long-term safety and effectiveness of this medication throughout the disease course in individuals with Huntington's disease-related chorea[22].

Section 3.0 Key Recommendations Synthesis

Diagnosis of HD:

- Traditionally, the clinical diagnosis of HD is based on the observation of involuntary movements in a patient with an appropriate family history, and supportive social history such as a decline in function or insidious onset of mood disturbance.
- The diagnosis should be confirmed by genetic testing; which is particularly useful when there is an unknown, or negative family history or when the family history is positive, but the symptoms are atypical.

Stages of HD:

- Huntington's Disease can be divided into three stages; early stage, middle stage and late stage HD.
- The Total Functional Capacity Rating Scale is a rating scale based on functional abilities that rates the patient's level of independence in five domains: occupation, ability to manage finances, ability to perform domestic chores, ability to perform personal activities of daily living, and setting for level of care.
- Some clinicians use the TFC score to determine the disease stage according to the Shoulson and Fahn rating scale.

Management of Motor Disorders:

- **Chorea:**
    - Tetrabenazine is a first line agent for the management of chorea. **(Grade A)**
    - Second generation neuroleptics are first-line treatments in patients who have associated personality and/or behavioral or psychotic disorders. **(Grade B)**
    - Monotherapy to treat chorea is preferred.
    - The following table depicts the agents used as anti-chorea therapy:

Medication	Initial dose	Maximal dose	Side effects
Tetrabenazine	12.5 mg	50 mg/day	Depression, akathisia, worsening of voluntary motor control Sedation
Haloperidol	0.5-1 mg	10-15 mg/day	Extrapyramidal syndrome (abnormal involuntary movements): akathisia, dystonia, bradykinesia Sedation
Fluphenazine	1-2 mg	10 mg/day	Extrapyramidal syndrome Sedation
Risperidone	0.5-1 mg	5-10 mg/day	Extrapyramidal syndrome at higher doses Sedation
Olanzapine	1.25-2.5 mg	10-15 mg/day	Extrapyramidal syndrome Sedation Weight gain and metabolic syndrome

- **Dystonia:**
  - Both active and passive physiotherapy approaches are recommended as a preventive measure to maintain the range of joint motion, limit postural and musculoskeletal deformities and prevent the development of contractures.
  - Injection of botulinum toxin in the case of focal dystonia or to prevent secondary deformities should be performed by a trained professional.
- **Rigidity:**
  - Rigidity may be increased or induced by the use of neuroleptics or tetrabenazine.
  - If this impacts the functional capacity of the patient, a reduction in dosage or the withdrawal of neuroleptics and/or tetrabenazine should be considered.
  - Levodopa may provide partial and temporary relief of the akinetic–rigid symptoms of HD, especially in juvenile forms. **(Grade C)**

    - Physiotherapy is recommended to improve or maintain mobility and prevent the development of contractures and joint deformity. **(Grade C)**

- **Bradykinesia:**
    - Anti-chorea therapy may unmask or worsen bradykinesia.
    - Bradykinesia in people with Juvenile onset HD, and adults with the rigid/dystonic form of HD, may improve with treatment using levodopa.
- **Tics:**
    - If severe, tics may be reduced by using benzodiazepines, SSRIs, neuroleptics and possibly by off-label use of tetrabenazine.
- **Akathisia:**
    - Tetrabenazine, neuroleptics and Selective serotonin reuptake inhibitors (SSRI) may cause akathisia in HD and reducing the dose or changing the treatment may be helpful. **(Grade C)**
- **Myoclonus:**
    - Treatment with sodium valproate or clonazepam, used alone or in combination, and in escalating doses, is recommended for the treatment of myoclonus. **(Grade C)**
    - Levetiracetam is a therapeutic alternative for the same indication.
    - In case of myoclonus of cortical origin that is not associated with epileptic seizures, piracetam has a marketing authorization. **(Grade C)**
- **Swallowing Disorders:**
    - The management of swallowing disorders in HD is based on clinical evaluation and swallowing assessment by expert opinion, and should involve advice on posture and installation, appropriate food texture, rehabilitation of facial oral praxis, pneumophonic coordination and the elimination of distraction factors. **(Grade C)**
    - No pharmacological treatment has proved effective for these disorders.
    - In advanced disease, percutaneous endoscopic gastrostomy feeding may be considered on a case-by-case basis.
- **Gait and Balance Impairment:**
    - Physiotherapy interventions **(Grade B)** and the introduction of falls prevention programs, gait, core stability, and balance interventions **(Grade C)** as well as attentional training are recommended.

    - Pharmaceutical management of chorea may improve walking and balance as they can be affected by chorea. **(Grade C)**
    - The use of assistive devices such as four-wheeled walker as recommended by Physiotherapist or Occupational Therapist should be considered to improve stability and reduce fall risk. **(Grade B)**
- **Bruxism:**
    - Injecting botulinum toxin A into the masseter muscles is proposed as the first-line treatment of bruxism. **(Grade C)**
    - Customized protective mouth guards may be used to reduce the complications of bruxism on a case-by-case basis, mostly in early stage patients.
    - Bruxism may occur as a side effect of neuroleptics **(Grade C)** and serotonin reuptake inhibitors, thus reducing their dose should be considered.
- **Manual Dexterity:**
    - Neuroleptics and tetrabenazine may possibly have a beneficial effect on dexterity as a result of reducing chorea. **(Grade C)**
    - Management with physiotherapy and occupational therapy may be useful to reduce the functional impact of fine motor skill deterioration. **(Grade B)**

No pharmacological treatment is available for the **management of cognitive disorders** in HD.

<u>Management of Psychiatric Disorders:</u>

- **Depression:**
    - It is recommended to use a selective SSRI or a serotonin noradrenaline reuptake inhibitor (SNRI), or alternatively Mianserin or Mirtazapine, in case of sleep disruption. **(Grade B)**
- **Irritability:**
    - In order to reduce irritability, behavioral strategies should be considered.
    - Whilst SSRIs are first lines for irritability, it may be necessary to use them at or near the maximum recommended dose in order to be effective. **(Grade C)**

    - Irritable patients who do not benefit from an SSRI alone may benefit from combination therapy with Mianserin or Mirtazapine, especially when sleep disorders are present.
    - In patients with aggressive behavior, the recommended first-line treatment is a neuroleptic. **(Grade C)**
    - In case of overt aggression associated with depression, neuroleptic treatment should be associated with sedative antidepressants.
    - If irritability does not respond to antidepressant therapies and/or neuroleptics, a mood stabilizer can be added. **(Grade C)**
- **Anxiety:**
    - SSRI or SNRI are first line treatments for anxiety, especially when associated with depression.
    - Neuroleptics are valuable therapeutic alternatives in the treatment of anxiety when other treatments fail. **(Grade C)**
- **Obsessions:**
    - If pharmacological treatment is necessary for perseverative symptoms, an SSRI could be prescribed. **(Grade C)**
    - Olanzapine and risperidone are two valuable therapeutics for ideational perseverations, in particular when they are associated with irritability.
    - If pharmacological treatment is necessary for obsessive-compulsive phenomena, a SSRI should be prescribed as first-line treatment. **(Grade C)**
- **Sexual Impairment:**
    - In case of impotence, prescription of phosphodiesterase 5 inhibitors should be considered.
    - If hypersexuality involves social discomfort or violence, the proposed first-line treatment is a neuroleptic and/or a SSRI. **(Grade C)**
    - If the treatment for hypersexuality with neuroleptics and/or SSRI is not successful, the addition of or substitution for an anti-androgen may be proposed. **(Grade C)**
- **Hallucinations:**
    - Second generation neuroleptics are the first line treatment for hallucinations and delusions. **(Grade C)**
    - Clozapine should be proposed as the first-line treatment in the case of akinetic forms of HD with debilitating Parkinsonian symptoms.

    - If pharmacological treatments fail, the option of ECT can be discussed with psychiatrists. **(Grade C)**

- **Agitation:**
    - When agitation is associated with an anxiety disorder, a benzodiazepine should be prescribed as needed to reduce the risk of dependence and falls. **(Professional agreement)**
    - Some benzodiazepines (e.g., midazolam) may be useful in emergency situations. **(Grade C)**
    - Long-term treatment with benzodiazepines should be avoided as much as possible but remains necessary in some patients. **(Grade C)**
    - In the case of extreme agitation, and if there are associated behavioral and personality disorders, it is advised to prescribe a neuroleptic. **(Grade C)**
- **Seizures:**
    - Seizures are more likely to occur in younger adults with HD.
    - Careful history and medical work-up is indicated, together with brain imaging and EEG.
    - If unprovoked seizures are suspected, pharmacologic treatment should be instituted based on the seizure type and concomitant medications.
- **Sleep Disorders:**
    - Simple lifestyle and dietary strategies (e.g., avoiding long naps, having no stimulants after 4 pm) are the first-line treatment of insomnia.
    - When lifestyle strategies are ineffective to treat insomnia, prescribing a hypnotic may be suggested for a short duration to avoid the risk of drug dependence.
    - Some agents may be proposed in place of a hypnotic and for a long duration (e.g., mianserin, mirtazapine, and antihistaminic drugs) as they have a reduced tendency for causing dependency.
    - Melatonin may be suggested in case of sleep phase inversion.
    - A neuroleptic should be prescribed in the evening when sleep disorders are associated with behavioral disorders or chorea.
- **Urinary Incontinence:**
    - Carbamazepine may be of benefit for diurnal unexpected complete urination. **(Grade C)**

    - In the case of an overactive bladder with leakage and urge incontinence, therapy with selective antimuscarinic may be tried, whilst watching out for the appearance of potential side effects, in particular confusional state.

- **Weight Loss:**
    - When weight loss is observed, high-calorie and high-protein food supplements should be prescribed under instruction and monitored by a dietician/nutritionist. **(Grade C)**
    - A Mediterranean diet may improve Quality of Life and nutritional composition. **(Grade C)**
    - In case of the initiation of antidepressant and/or neuroleptic treatments, treatments inducing weight gain should be preferred in patients with significant weight loss, whilst treatments inducing weight loss should be avoided. **(Grade C)**
- **Hypersalivation:**
    - In the absence of a specific treatment for HD, drugs used in other chronic diseases may be considered to reduce salivary secretion: scopolamine given percutaneously, atropine given orally or other drugs that have an anticholinergic effect (amitriptyline), whilst watching out for iatrogenic risks, in particular confusional state, constipation, ocular hypertension and urinary retention.
    - Injections of botulinum toxin into the salivary glands may be considered in a specialized setting if oral or oral mucosa treatment options have not induced benefit or were not well-tolerated.

Genetic Counseling:

Genetic counseling is an essential part of HD management, whereby the genetic counsellor will discuss the implications of a diagnosis of HD on the patient and their family. A genetic counselling team will provide support for concerned parties; this would include providing testing to asymptomatic adult siblings and potentially, prenatal testing.

Management of Juvenile Onset Huntington's Disease:

- **Treatments and Therapies for the Movement Disorder:** No medications improve control of voluntary movements, although there are treatments for rigidity, spasticity, dystonia, and chorea that may help children with JHD as mentioned above.

- **Treatments and Therapies for Cognitive Disorders:** No medications have been proven to improve cognitive function in HD.

  If frequent seizures, attention deficit, or depression are interfering with a child's ability to perform, treating these symptoms may improve the child's quality of life.

- **Treatments and Therapies for Psychiatric Disorders:**
  - **Depression:**
    - SSRIs are the most commonly used in recent years, because of their favorable side effect profile. No antidepressant is specifically preferred over others in HD patients.
    - The following antidepressants are frequently used in practice: Tricyclic antidepressants (Amitriptyline, Nortriptyline, Imipramine, Clomipramine), Selective serotonin reuptake inhibitors (Fluoxetine, Sertraline, Citalopram, Escitalopram, Paroxetine), Serotonin-norepinephrine reuptake inhibitors (Venlafaxine, Bupropion) and other agents include Trazodone and Mirtazapine.
  - **Aggressive, Explosive or Violent Behavior:**
    - Potential agents that may be used include mood stabilizers such as valproic acid and lamotrigine, antipsychotic agents such as haloperidol, olanzapine, or risperidone, sedatives such as lorazepam or clonazepam, or beta-adrenergic blockers such as propranolol.
    - Some children may have attention deficit disorder or hyperactivity in addition to HD; For these children, treating these symptoms may lead to an improvement in behavior.
  - **Obsession:**
    - Behavioral modification strategies may be opted for the management of obsession.
    - Medications such as SSRIs or clomipramine can be used to suppress obsessive thoughts.
  - **Hallucinations:**
    - The mainstay of treatment for hallucinations and for delirium are the antipsychotic or neuroleptic drugs.
    - Older antipsychotic drugs include haloperidol, thorazine, and fluphenazine, among many others.

        - A newer group of “selective” antipsychotics, designed to have fewer side effects, includes risperidone, olanzapine, clozapine, and quetiapine, among others.
    - **Seizures:**
        - Children with HD who have seizures usually have generalized or myoclonic epilepsy, although other seizure types are possible (focal or partial complex seizures).
        - Valproic acid and lamotrigine are considered first choices for the treatment of myoclonic epilepsy.
        - Phenytoin, carbamazepine, levetiracetam, topiramate, and zonisamide are among the favored drugs; the selection of a medication should be made carefully after the evaluation is completed.

Section 4.0 Conclusion

The recommendations provided in this report are intended to assist in the management of Huntington’s Disease.

These recommendations should be used to support and not supplant decisions in individual patient management.

Section 5.0 References

1. Huntington Disease Continuing Education Activity. Published July 2023. Accessed October 2, 2023. https://www.ncbi.nlm.nih.gov/books/NBK559166/
2. Medina A, Mahjoub Y, Shaver L, Pringsheim T. Prevalence and Incidence of Huntington's Disease: An Updated Systematic Review and Meta-Analysis. *Movement Disorders*. 2022;37(12):2327-2335. doi:10.1002/mds.29228
3. Squitieri F, Maffi S, Al Harasi S, et al. Incidence and prevalence of Huntington disease (HD) in the Sultanate of Oman: the first Middle East post-HTT service-based study. *J Neurol Neurosurg Psychiatry*. 2020;91(12):1359-1360. doi:10.1136/jnnp-2020-323241
4. 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. doi:10.1016/S1474-4422(22)00120-X
5. Huntington's Disease Complications. Published 2010. Accessed October 3, 2023. https://hopes.stanford.edu/complications-of-huntingtons-disease/
6. HD Therapies in Pipeline. Published 2023. Accessed October 22, 2023. https://hdsa.org/hd-research/therapies-in-pipeline/
7. A gene therapy hope for halting Huntington's disease | Drug Discovery News. Accessed October 23, 2023. https://www.drugdiscoverynews.com/a-gene-therapy-hope-for-halting-huntington-s-disease-15759
8. Coppen EM, Roos RAC. Current Pharmacological Approaches to Reduce Chorea in Huntington's Disease. *Drugs*. 2017;77(1):29-46. doi:10.1007/s40265-016-0670-4
9. Gupta H, Perkins W, Stark C, et al. deutetrabenazine for the treatment of chorea associated with Huntington's disease. *Health Psychol Res*. 2022;10(2):1-9. doi:10.52965/001c.36040
10. Fda. *HIGHLIGHTS OF PRESCRIBING INFORMATION*. www.fda.gov/medwatch.
11. Stahl SM. Mechanism of action of vesicular monoamine transporter 2 (VMAT2) inhibitors in tardive dyskinesia: reducing dopamine leads to less "go" and more "stop" from the motor striatum for robust therapeutic effects. *CNS Spectr*. 2018;23(1):1-6. doi:10.1017/S1092852917000621
12. Bachoud-Lévi AC, Ferreira J, Massart R, et al. International guidelines for the treatment of Huntington's disease. *Front Neurol*. 2019;10(JUL). doi:10.3389/fneur.2019.00710

13. Anderson KE, Van Duijn E, Craufurd D, et al. Clinical management of neuropsychiatric symptoms of huntington disease: Expert-based consensus guidelines on agitation, anxiety, apathy, psychosis and sleep disorders. *J Huntingtons Dis*. 2018;7(4):355-366. doi:10.3233/JHD-180293

14. Nance M, Paulsen JS, Rosenblatt A, Wheelock V. *Third Edition A Physician's Guide to the Management of Huntington's Disease*.

15. Nance M. *The Juvenile HD Handbook A Guide for Families and Caregivers-SECOND EDITION*.; 2007.

16. Armstrong MJ, Miyasaki JM. *Evidence-Based Guideline: Pharmacologic Treatment of Chorea in Huntington Disease*.; 2012. www.neurology.org

17. Désaméricq G, Youssov K, Charles P, et al. Guidelines for clinical pharmacological practices in Huntington's disease. *Rev Neurol (Paris)*. 2016;172(8-9):423-432. doi:10.1016/j.neurol.2016.07.012

18. Clark ML, Abimanyi-Ochom J, Le H, Long B, Orr C, Khanh-Dao Le L. A systematic review and meta-analysis of depression and apathy frequency in adult-onset Huntington's disease. *Neurosci Biobehav Rev*. 2023;149. doi:10.1016/j.neubiorev.2023.105166

19. Chen S, Liang T, Xue T, Xue S, Xue Q. Pridopidine for the Improvement of Motor Function in Patients With Huntington's Disease: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Front Neurol*. 2021;12. doi:10.3389/fneur.2021.658123

20. apegorier. *HAS-Direction de l'Evaluation Médicale, Economique et de Santé Publique COMMISSION DE LA TRANSPARENCE*.

21. deutetrabenazine-psd-mar-2021 (1).

22. 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. doi:10.1016/S1474-4422(23)00127-8

Section 6.0 Appendices

Appendix A. Prescribing Edits Definition

Some covered drugs may have additional requirements, rules, or limits on coverage. These requirements and limits may include:

Prescribing edits Tools	Description
AGE (Age):	Coverage may depend on patient age
CU (Concurrent Use):	Coverage may depend upon concurrent use of another drug
G (Gender):	Coverage may depend on patient gender
MD (Physician Specialty):	Coverage may depend on prescribing physician's specialty or board certification
PA (Prior Authorization):	Requires specific physician request process
QL (Quantity Limits):	Coverage may be limited to specific quantities per prescription and/or time period
ST (Step Therapy):	Coverage may depend on previous use of another drug
EU (Emergency Use only):	This drug status on Formulary is only for emergency use
PE (Protocol Edit):	Use of drug is dependent on protocol combination, doses and sequence of therapy

Appendix B. Level of Evidence Description

Grade of research	
A	Strongly recommend; good evidence
B	Recommend; at least fair evidence
C	No recommendation for or against; balance of benefits and harms too close to justify a recommendation
D	Recommend against; fair evidence is ineffective, or harm outweighs the benefit
E	Evidence is insufficient to recommend for or against routinely; evidence is lacking or of poor quality; benefits and harms cannot be determined
Level of evidence	
Level I	Meta-analysis of multiple studies
Level II	Experimental studies
Level III	Well-designed, quasi-experimental studies
Level IV	Well-designed, non-experimental studies
Level V	Case reports and clinical examples

Appendix C. PubMed Search Methodology Terms

The following PubMed Search Methodology was opted:

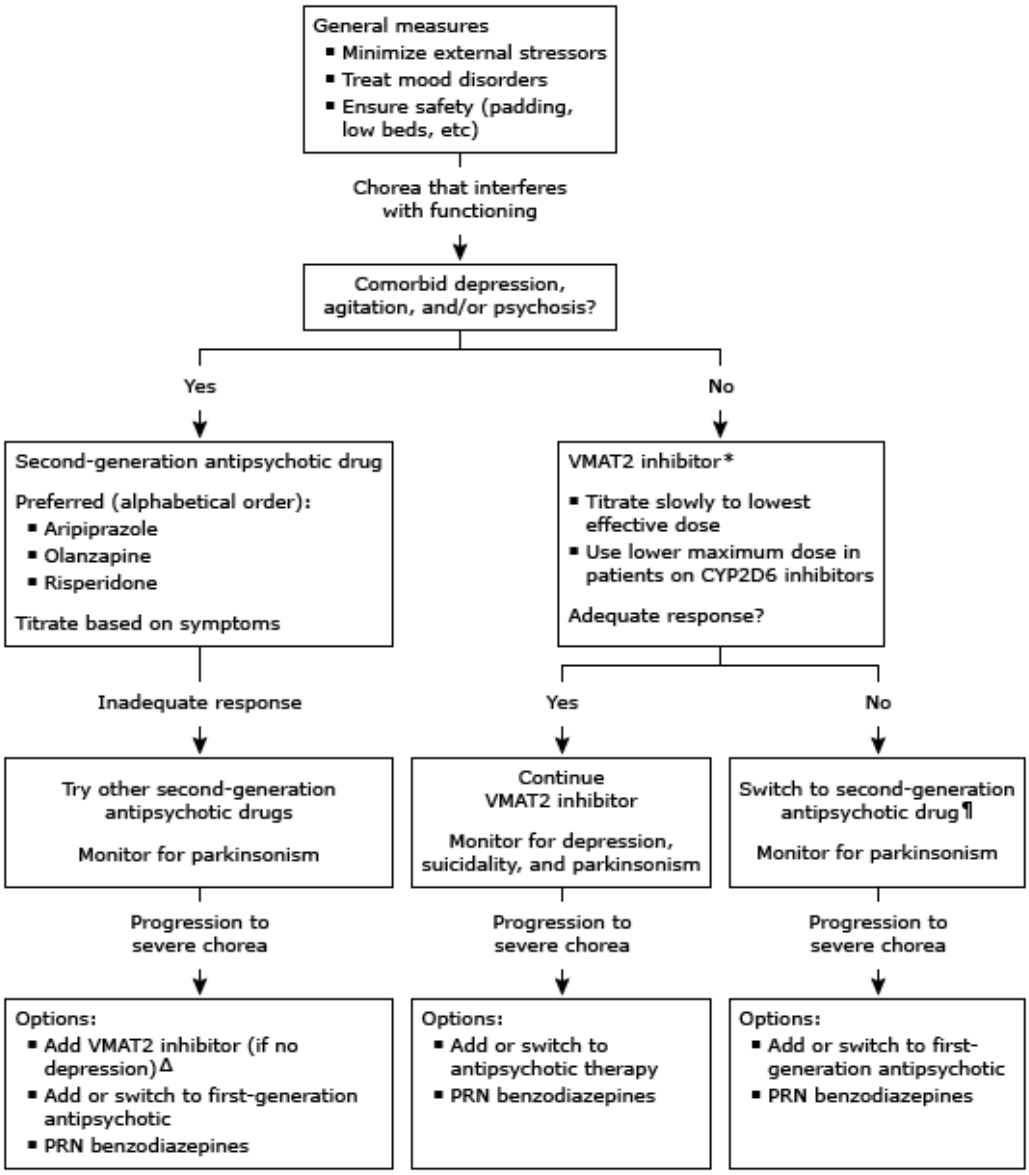
Query	Filters	Search Details	Results
((((((((((((((((((((((Huntington Disease[MeSH Terms]) OR (Huntington Chorea[Title/Abstract])) OR (Chorea, Huntington[Title/Abstract])) OR (Huntington's Disease[Title/Abstract])) OR (Chronic Progressive Hereditary Chorea (Huntington[Title/Abstract]))) OR (Huntington Chronic Progressive Hereditary Chorea[Title/Abstract])) OR (Progressive Chorea, Chronic Hereditary (Huntington[Title/Abstract]))) OR (Progressive Chorea, Hereditary, Chronic (Huntington[Title/Abstract]))) OR (Huntington's Chorea[Title/Abstract])) OR (Chorea, Huntington's[Title/Abstract])) OR (Chorea, Chronic Progressive Hereditary (Huntington[Title/Abstract]))) OR (Huntington Disease, Late Onset[Title/Abstract])) OR (Late-Onset Huntington Disease[Title/Abstract])) OR (Huntington Disease,	Guideline, in the last 5 years	("huntington disease"[MeSH Terms] OR "huntington chorea"[Title/Abstract] OR "chorea huntington"[Title/Abstract] OR "huntington s disease"[Title/Abstract] OR (("huntington disease"[MeSH Terms] OR ("Huntington"[All Fields] AND "Disease"[All Fields]) OR "huntington disease"[All Fields] OR ("Chronic"[All Fields] AND "Progressive"[All Fields] AND "Hereditary"[All Fields] AND "Chorea"[All Fields]) OR "chronic progressive hereditary chorea"[All Fields]) AND "Huntington"[Title/Abstract]) OR (("Huntington"[All Fields] OR "Huntington's"[All Fields] OR "huntingtons"[All Fields]) AND "chronic progressive hereditary chorea"[Title/Abstract]) OR ((("Chorea"[MeSH Terms] OR "Chorea"[All Fields] OR ("Progressive"[All Fields] AND "Chorea"[All Fields] AND "Chronic"[All Fields])) AND "Hereditary"[All Fields]) AND "Huntington"[Title/Abstract]) OR ((("disease progression"[MeSH Terms] OR ("Disease"[All Fields] AND "progression"[All Fields]) OR "disease progression"[All Fields]	2

Late-Onset[Title/Abstract])) OR (Late Onset Huntington Disease[Title/Abstract])) OR (Juvenile Huntington Disease[Title/Abstract])) OR (Juvenile-Onset Huntington Disease[Title/Abstract])) OR (Juvenile Onset Huntington Disease[Title/Abstract])) OR (Huntington Disease, Juvenile-Onset[Title/Abstract])) OR (Huntington Disease, Juvenile Onset[Title/Abstract])) OR (Huntington Disease, Juvenile[Title/Abstract])) OR (Akinetic-Rigid Variant of Huntington Disease[Title/Abstract])) OR (Akinetic Rigid Variant of Huntington Disease[Title/Abstract])) OR (Huntington Disease, Akinetic-Rigid Variant[Title/Abstract])) OR (Huntington Disease, Akinetic Rigid Variant[Title/Abstract])		OR "progression"[All Fields] OR "progress"[All Fields] OR "progressed"[All Fields] OR "progresses"[All Fields] OR "progressing"[All Fields] OR "progressions"[All Fields] OR "Progressive"[All Fields] OR "progressively"[All Fields] OR "progressives"[All Fields]) AND ("Chorea"[MeSH Terms] OR "Chorea"[All Fields] OR ("Chorea"[All Fields] AND "Hereditary"[All Fields]) OR "chorea hereditary"[All Fields]) AND ("Chronic"[All Fields] OR "chronical"[All Fields] OR "chronically"[All Fields] OR "chronicities"[All Fields] OR "chronicity"[All Fields] OR "chronicization"[All Fields] OR "chronics"[All Fields])) AND "Huntington"[Title/Abstract]) OR "huntington s chorea"[Title/Abstract] OR "chorea huntington s"[Title/Abstract] OR (("huntington disease"[MeSH Terms] OR ("Huntington"[All Fields] AND "Disease"[All Fields]) OR "huntington disease"[All Fields] OR ("Chorea"[All Fields] AND "Chronic"[All Fields] AND "Progressive"[All Fields] AND "Hereditary"[All Fields])) AND "Huntington"[Title/Abstract]) OR (("Huntington"[All Fields] OR "Huntington's"[All Fields] OR "huntingtons"[All Fields]) AND "disease late onset"[Title/Abstract]) OR "late	

		onset huntington disease"[Title/Abstract] OR (("Huntington"[All Fields] OR "Huntington's"[All Fields] OR "huntingtons"[All Fields]) AND "disease late onset"[Title/Abstract]) OR "late onset huntington disease"[Title/Abstract] OR "juvenile huntington disease"[Title/Abstract] OR "juvenile onset huntington disease"[Title/Abstract] OR "juvenile onset huntington disease"[Title/Abstract] OR (("huntington disease"[MeSH Terms] OR ("Huntington"[All Fields] AND "Disease"[All Fields]) OR "huntington disease"[All Fields]) AND "Juvenile-Onset"[Title/Abstract]) OR (("huntington disease"[MeSH Terms] OR ("Huntington"[All Fields] AND "Disease"[All Fields]) OR "huntington disease"[All Fields]) AND "Juvenile-Onset"[Title/Abstract]) OR "huntington disease juvenile"[Title/Abstract] OR (("Akinetic-Rigid"[All Fields] AND ("Variant"[All Fields] OR "variant s"[All Fields] OR "variants"[All Fields])) AND "of huntington disease"[Title/Abstract]) OR (("Akinetic"[All Fields] AND ("muscle rigidity"[MeSH Terms] OR ("muscle"[All Fields] AND "rigidity"[All Fields]) OR	

		"muscle rigidity"[All Fields] OR "Rigid"[All Fields] OR "rigidity"[All Fields] OR "rigidities"[All Fields] OR "rigidness"[All Fields]) AND ("Variant"[All Fields] OR "variants"[All Fields] OR "variants"[All Fields])) AND "of huntington disease"[Title/Abstract]) OR (("huntington disease"[MeSH Terms] OR ("Huntington"[All Fields] AND "Disease"[All Fields]) OR "huntington disease"[All Fields]) AND "akinetic rigid variant"[Title/Abstract]) OR (("huntington disease"[MeSH Terms] OR ("Huntington"[All Fields] AND "Disease"[All Fields]) OR "huntington disease"[All Fields]) AND "akinetic rigid variant"[Title/Abstract])) AND ((y_5[Filter]) AND (guideline[Filter]))	

Appendix D. Treatment Algorithm



VMAT2: vesicular monoamine transporter type 2; CYP2D6: cytochrome P450 2D6; PRN: as needed.

* VMAT2 inhibitors approved for use in patients with Huntington disease are tetrabenazine, deutetrabenazine, and valbenazine. Deutetrabenazine and valbenazine have longer half-lives. Availability and cost may vary by region.

¶ When switching from a VMAT2 inhibitor to antipsychotic therapy, begin antipsychotic therapy and then gradually taper VMAT2 inhibitor. Preferred second-generation antipsychotic drugs for chorea are aripiprazole, olanzapine, and risperidone.

Δ Some experts may consider a VMAT2 inhibitor in patients with comorbid depression who have refractory chorea; others consider depression a strict contraindication to VMAT2 inhibitor use in this population.

Figure 2. *Treatment Algorithm for the Management of Chorea in Patients with Huntington's Disease*