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State-of-the-art pharmacological approaches to reduce chorea in Huntington's Disease

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Abstract

Introduction—Chorea is a common motor manifestation of Huntington's disease (HD). Two vesicular monoamine transporter type 2 (VMAT-2) inhibitors have been approved by the FDA for treatment of HD chorea, and a third is currently being assessed in a phase 3 trial. Antipsychotic therapies are used off-label for treatment of chorea and can treat comorbid psychiatric symptoms. There is considerable clinical equipoise regarding the safe and effective treatment of chorea and comorbid symptoms in HD.

Areas covered: The authors review existing medications used to treat HD chorea in the United States of America (USA). Implications for common comorbid symptoms (e.g. psychiatric, metabolic) are also discussed. Available therapies vary widely in cost, dosing frequency, and off - target effects, both beneficial or negative.

Expert opinion: Treatment considerations for chorea should account for patient comorbidities. The authors recommend prospective, observational clinical effectiveness studies which can evaluate the long-term comparative effectiveness and safety of VMAT-2 inhibitors and antipsychotics in HD. Data regarding safety of dual therapy is another critical need. This is especially timely given the changing landscape of HD therapies which may increase cost burden and possibly extend both asymptomatic and symptomatic years for HD patients.

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Keywords

Huntington Disease; Chorea; Tetrabenazine; Antipsychotic Agents; Off-Label Use; Clinical Decision-Making

1.0 Introduction

Huntington's disease (HD) is an autosomal dominant, neurodegenerative disease caused by an expansion of CAG trinucleotide repeats on chromosome 4. HD is characterized by abnormal involuntary movements, cognitive decline, and behavior changes. Chorea is the most prominent symptom of HD, and average onset is in the 4th or 5th decade of life. In 1872, George Huntington published an early description of chorea as an irregular, spasmodic dance-like movement that, in HD, progresses to every voluntary muscle in the body [1]. In the following years, the disease was called "Huntington's chorea", and not for another century did "Huntington's disease" become more-widely used, acknowledging that HD is typified by more than chorea alone. Even so, chorea remains a focal component of modern HD treatment and investigation. In fact, participation in most HD clinical trials hinges on a diagnosis of "motor-manifest" HD. In the years since HD was first described, a number of advances have been made. Most notable was the isolation of the HD gene in 1993. Since that time, breakthroughs have come in the form of pharmacological treatments to reduce chorea. Here we aim to describe HD chorea and approaches for management, as well as promising directions in HD research.

2.0 Chorea: an overview

Patients with HD can display a variety of abnormal movements related to disruption of basal ganglia circuits. Briefly, there is significant early loss of medium spiny neurons (MSN) in the striatal pathways connected with the external Globus Pallidus (GP), which express predominantly D2 receptors [2]. It is thought that this loss leads to chorea in early HD, whereas eventual degradation of MSNs expressing primarily D1 in the direct pathway (internal GP and subtantia nigra) lead to akinetic motor symptoms seen later in HD [3].

As described, chorea is the most common motor manifestation of HD. Dystonia is also common in HD and includes sustained involuntary muscle contractions often resulting in abnormal posturing [4]. Possibly due to direct pathway dysfunction, dystonia severity tends to increase with disease stage and duration of motor symptoms in HD patients [5], whereas chorea is thought to reduce in severity in late-stage disease. Tremor, myoclonus, tics, and ataxia are also seen in HD, though most often in persons with juvenile onset [6–9].

The spectrum of dyskinesias includes chorea, athetosis, and ballism. These movements share similar pathogeneses related to disruption of the indirect pathway, decreased inhibition in the pallidum, and increased striatal dopamine receptor activity [10]. Ballism refers to large, proximal choreatic movements, whereas athetosis describes irregular writhing movements most often observed in the distal extremities [10]. When chorea is rated clinically, it is often conflated with ballism and athetosis.

In persons with HD, chorea causes significant functional limitations. Loss of autonomy is of particular concern, as persons with HD become progressively dependent, eventually losing the ability to work, drive, and perform activities of daily living (ADLs) such as household chores and personal grooming [11]. Although other features of HD, such as cognitive and neuropsychiatric symptoms, also contribute to functional decline, chorea itself can be disabling. Gait disturbance and falls are often attributed to chorea, as are dysphagia and dexterity issues [12]. In addition to functional limitations, chorea negatively affects health-related quality of life [12]. For example, patients may feel stigmatized when their abnormal movements are misinterpreted as drunkenness [11], and stigma and anxiety are higher in patients with more chorea [12]. It should be noted, however, that many HD patients exhibit anosognosia and are unaware of the presence or severity of their HD symptoms [13, 14]. In these circumstances, caregivers are most impacted by chorea. One survey of HD patients and caregivers found that 30 percent of caregivers identified chorea as the most impactful symptom of HD, compared to only 17 percent of HD patients [15]. Despite anosognosia, and considering the widespread effects of chorea, a majority of HD patients (59%) and caregivers (71%) reported that management of chorea was very important to their care [12].

Chorea is quantified using clinical rating scales such as the United Huntington's Disease Rating Scale Total Motor Score (UHDRS-TMS) or similar observational scales [16, 17]. UHDRS-TMS is a a semi-structured, focused neurologic examination. For the chorea subscale of the UHDRS-TMS, clinicians use an ordinal scale to rate severity of facial, buccal-oral-lingual, trunk, and extremity chorea. The chorea subscale of the UHDRS-TMS has been used in clinical trials as a primary endpoint for chorea reduction [18, 19]. Despite its frequent use, the subjective and categorical nature of UHDRS-TMS has generated concern regarding its reliability and sensitivity to change [20]. Significant inter-rater variability has been seen in observational ratings of chorea, and it has been suggested that UHDRS chorea ratings are more reliable in HD patients with significant motor burden as opposed to those with pre-manifest and prodromal disease [21]. However, in a Movement Disorder Society commissioned review, UHDRS-TMS was the only clinical rating scale recommended (versus suggested) for motor symptom assessment in HD [22].

Quantitative motor (Q-Motor) assessments of chorea have been proposed to address limitations of the UHDRS [20]. For the Q-Motor chorea position and orientation indices, patients are instructed to grip and hold static an instrument containing movement-tracking sensors [20]. These measures overcome some of the limitations of the UHDRS, though evidence of their utility in premanifest HD patients is mixed [23, 24]. Additionally, mild chorea can be voluntarily suppressed and tends to emerge with distraction [25]. Because these indices measure chorea in performance of a specific task, they may miss chorea which emerges at rest or with distraction. Furthermore, non-extremity chorea may be missed using Q-Motor assessments.

Severity of chorea may vary depending on circumstances, further limiting the effectiveness of chorea assessment at a single timepoint (i.e. during a clinic or research visit). For example, nocturnal choreatic movements are a key component of sleep disturbance in HD [26–28] and may represent a very early motor manifestation of HD [29]. Psychiatric disturbances

such as anxiety can also worsen chorea, so situational differences (e.g. level of comfort with a clinician) can influence chorea ratings that are done at a single time point.

A novel form of chorea assessment has been piloted, using wearable, accelerometer-based sensors applied directly to a patient's trunk and extremities or worn as a watch [30, 31]. These sensors allow for continuous measurement of movements, even in sleep, compensating for limitations of the previous assessment methods. While constraints of sensor-based measurement certainly exist (e.g. patient comfort and long-term sensor adhesion [32], measurement of oral-facial chorea), it represents an exciting new vehicle for measuring chorea in its diverse forms.

3.0 Comorbidities and treatment considerations

The primary comorbidities of chorea and motor dysfunction in HD include cognitive and neuropsychiatric symptoms. Weight loss, dysphagia, sleep disturbance, and communication difficulties are similarly common manifestations. Although the presentation of HD can vary between and within patients over the course of disease progression, these comorbidities are expected to occur at some point in most patients. Thus, treatment decisions for chorea are often influenced by the nature of comorbid symptoms.

As an example, anxiety is a common neuropsychiatric manifestation which has been associated with chorea and may worsen chorea's impact on health-related quality of life [12]. In this event, treatment for underlying anxiety may influence presentation of chorea over and above the influence of antichoreatic medications. Anxiety may be reduced through pharmacological or non-pharmacological methods (e.g. adherence to a routine), so such interventions should be considered in a patient with treatment-resistant chorea or contraindication to certain antichoreatic medications. For example, antipsychotic medications may be considered in patients exhibiting concurrent psychiatric symptoms and chorea, while VMAT-2 inhibitors should be avoided in patients with uncontrolled depression or suicidality. Further, stimulant medications should be used with caution in HD due to concern due to concern for exacerbating chorea [33, 34] or hastening disease progression. While the pathophysiologic basis for stimulant use and motor progression is unclear, likely augmentation of monoamines, especially dopamine, may be the basis for this clinical observation [34, 35]. On the other hand, because neuropsychiatric and cognitive symptoms may have higher relative impact on HD patients [36], providers may choose to prioritize treating these non-motor symptoms over chorea.

Although neuropsychiatric comorbidities often have the greatest influence in treatment of chorea, other disease manifestations similarly impact treatment decisions. Choice of antichoreatic regimen and/or dose timing may be done to maximize the benefit of side effects (i.e. somnolence, weight gain) for patients with altered sleep-wake cycle or weight loss. Cognitive decline may similarly influence treatment decisions, as antidopaminergic medications may be linked to worsening cognition [37]. Medications requiring less frequent dosing (i.e. once daily versus three times a day) may be preferred in patients with anosognosia or who are noncompliant related to executive dysfunction or memory deficits. Dysphagia may similarly necessitate less frequent dosing or use of an agent which can be

crushed. Finally, hypokinetic or bradykinetic speech patterns have been associated with use of antichoreatic medications [38]. This may influence treatment decisions in patients whose occupation or social obligations require greater intelligibility.

4.0 Current pharmacological approaches to reduce chorea

Current pharmacological approaches to reduce chorea include dopamine receptor antagonists and vesicular monoamine transporter type 2 (VMAT-2) inhibitors (Table 1).

4.1 Antipsychotics

In the United States, dopamine receptor antagonists include first and second-generation antipsychotics. As described above, antipsychotic medications are often preferred for use in patients with comorbid psychiatric symptoms. Unfortunately, there are no controlled trials to guide use of antipsychotics in HD, and prescribing practices vary widely in the United States (US) and abroad [39, 40].

Antipsychotics are thought to reduce chorea through blockade of D2 receptors, attenuating hypersensitive striatal dopamine receptor sensitivity resulting from loss of MSNs. Prescribers and patients have relatively easy access to antipsychotics given their generic availability and lower cost relative to VMAT-2 inhibitors (see Table 1) [41]. First generation antipsychotics such as haloperidol may have benefits for chorea through strong D2 affinity, but adverse effects such as tardive dyskinesia, bradykinesia, and akathisia are thought to be greater than with second-generation antipsychotics [42, 43]. Outside the US, pimozide and benazmides (i.e. tiapride, amsulpiride, sulpiride) have been shown to reduce chorea [44–46], though they have less benefit for psychiatric symptoms and have been associated with worse cognitive outcomes than VMAT-2 inhibitors and other antipsychotics [47]. For these reasons, first generation antipsychotics are rarely used in contemporary HD treatment. Second-generation antipsychotics are more commonly used for treatment of chorea. The greatest number of reports have described the beneficial use of risperidone [48–55] olanzapine [56–65] and aripiprazole [66–71] for motor symptoms in HD. Notably, most of these were case reports, and prospective studies supporting safe and effective use of these medications are lacking.

Prior reports in HD patients consistently describe benefits of risperidone for chorea or involuntary movements [48–55] and delusional symptoms [48, 49, 54, 72–74]. This may be related to the higher potency of D2, D3, and 5HT2A receptor antagonism, as compared to olanzapine and aripiprazole [75]. These receptors localize in greater density to the mesolimbic pathway, a region linked to the onset of psychotic manifestations [76], and striatum, which is linked to chorea [77]. Greater dopamine antagonism in these areas likely explains risperidone's benefit in HD. However, compared to olanzapine and aripiprazole risperidone has also been associated with a higher prevalence of tardive syndromes including parkinsonism, akathisia, and dystonia [43].

Olanzapine has been reported to benefit HD patients with various motor and psychiatric symptoms [56, 58, 60–65]. However, compared with risperidone and aripiprazole, olanzapine carries a greater risk of weight gain in the general population [78] and can cause somnolence [79]. This is likely due to greater H1 receptor affinity [75] along with its well-known 5HT2A and

D2 receptor antagonism. Weight gain and somnolence could be considered adverse effects and limit tolerability and use of olanzapine in HD [63, 80]. Yet, for some patients with HD, clinicians will often prescribe this medication in order to achieve a higher body mass index (BMI). More importantly, the sedative effects of this medication can improve sleep [81], thus may provide unique benefit to patients.

Several reports in HD patients have described chorea improvement using aripiprazole [66–71].

Small studies have also shown potential clinical benefits of aripiprazole for apathy, anxiety and depression [67], aggression [68], and irritability [71]. This medication differs from the purely antagonistic D2 effects of olanzapine and risperidone, and it is hypothesized that its benefits are related to partial agonist effects on 5HT1A and D2-receptors, along with 5HT2A antagonism [75, 82].

Clozapine has shown benefit for reduction of motor symptoms of HD, but adverse effects and the need for repeated blood draws result in frequent discontinuation [83, 84]. Similarly, use of quetiapine has been described in three HD case reports [85–87] but with little evidence of chorea improvement. Interestingly, in a recent survey, US physicians reported using aripiprazole and olanzapine less frequently than quetiapine, clozapine, and even haloperidol [39], highlighting the lack of consensus regarding use of antipsychotics in HD.

4.2 VMAT-2 inhibitors

VMAT-2 inhibitors deplete vesicular monoamines (e.g. dopamine), preventing their release from presynaptic vesicles [88]. This is thought to prevent dopamine from reaching upregulated D2 receptors, thereby reducing chorea. Tetrabenazine was the first VMAT-2 inhibitor to be approved, and it has been indicated for the treatment of HD chorea in the US since 2008 [88]. It is worth noting that reserpine was another early VMAT inhibitor which bound irreversibly to VMAT-1 and VMAT-2 receptors, causing long-lasting off-target effects such as hypotension and depression, and limiting its further use [18, 89]. For years, tetrabenazine was the only medication approved by the FDA to treat HD chorea, and this is reflected in its continued frequent use by HD physicians [39]. Tetrabenazine is shown to be effective for reducing chorea severity in HD, though it is also associated with significant adverse effects including somnolence, akathisia, depression, and elevated risk for suicidality [18]. Tetrabenazine carries a black box warning for increased risk of suicidality in patients with HD, possibly due to off-target depletion of 5-HT and NE, and it is contraindicated in patients with uncontrolled depression [88]. However, some have argued that this in an over-cautious statement based on a small effect in a single trial, as follow-up analyses with larger samples have not found evidence of this risk [90, 91]. Major metabolites of tetrabenazine have half-lives between 7–12 hours, and it is recommended to be taken in divided doses up to three times per day [92].

Deutetrabenazine is VMAT-2 inhibitor that was approved for HD chorea in the US in 2017 and is also indicated for treatment of tardive dyskinesia [93]. The half-life of deutetrabenazine is extended through addition of deuterium atoms which create a stronger hydrogen carbon bond [88]. This allows for less frequent dosing (twice a day) and an improved tolerability compared to tetrabenazine [94]. Like tetrabenazine, deutetrabenazine carries a black box

warning for suicidality, though there was no indication of increased risk for depression or suicide compared to placebo in clinical trials of deutetrabenazine [19].

Valbenazine is a VMAT-2 inhibitor which, like deutetrabenazine, is indicated for treatment of tardive dyskinesia [95]. Valbenazine has not yet been approved by the FDA for treatment of HD chorea, but trials are ongoing (NCT04102579). Valbenazine is a prodrug of a major tetrabenazine metabolite and is dosed once a day. Unlike deutetrabenazine and tetrabenazine, doses for valbenazine are more strictly defined (i.e. recommend 80 mg daily vs a dosing range based on patient response). Reported side effects in clinical trials have been similar between valbenazine and deutetrabenazine, with somnolence being the most common adverse reaction [93, 95]. If proven to be effective in HD patients, this may represent an additional antichoreatic option for patients who struggle with medication compliance or who have had inadequate responses to existing VMAT-2 inhibitors.

There have been no prospective randomized controlled trials or observational comparative effectiveness studies to directly compare VMAT-2 inhibitors in HD patients. However, indirect comparisons of tetrabenazine and deutetrabenazine have concluded that deutetrabenazine may be associated with lower risk for depression and somnolence compared to tetrabenazine [94, 96]. Additionally, in a small open-label study of conversion from tetrabenazine to deutetrabenazine, HD patients had improved chorea control on deutetrabenazine compared to baseline (tetrabenazine) [97].

It should be noted that all VMAT-2 inhibitors are metabolized in the liver via CYP2D6 [92, 93, 95]. Several medications used to treat symptoms associated with HD are CYP2D6 inhibitors (e.g. antidepressants including fluoxetine or paroxetine), and it is recommended that prescribers carefully review and adjust concomitant medications as needed before initiating VMAT-2 inhibitor therapy. This is particularly relevant given the warning for increased risk of depression and suicidality with VMAT-2 inhibitors. Although it is unrealistic to avoid VMAT-2 inhibitor use in all patients with a history of depression (which may be seen in the majority of HD patients over time [98]), it is recommended that depression be adequately treated prior to starting VMAT-2 therapy. Thus, clinicians anticipating future use of a VMAT-2 inhibitor, perhaps in a patient with prodromal HD, may consider use of medications without CYP2D6 action.

4.3 Dual therapy

It is common for clinicians to prescribe multiple medications for treatment of chorea [99]. As may be expected, VMAT-2 inhibitors and antipsychotics are prescribed concurrently in clinical practice, either for treatment-resistant chorea or to address comorbid symptoms [99]. Though this is commonly done, there is little evidence to advise prescribers on which combinations of medications from these classes are safest and most effective according to individual patient characteristics. Indeed, it is likely that additive effects increase risks which are already present with use of individual anti-dopaminergic agents (e.g. QTc prolongation, neuroleptic malignant syndrome, cognitive decline [37]). Studies are needed which prospectively assess safety and efficacy of concurrent VMAT-2 inhibitor and antipsychotic use in a large sample.

5.0 Alternative and investigative antichoreatic treatments

5.1 Alternatives

Benzodiazepines (primarily clonazepam) [64, 99], antiepileptic medications [61, 100], and amantadine [101, 102] are sometimes used for treatment of HD chorea, though most commonly adjunctive to antipsychotic or VMAT-2 treatment [99]. In general, dose-limiting side effects (e.g. somnolence) and lack of rigorous efficacy data prevent these medications from being used as monotherapy for chorea.

5.2 Pridopidine

Pridopidine is an investigational dopamine stabilizer for which evidence of an antichoreatic effect is mixed [103–106]. A phase 3 clinical trial is planned in persons with early manifest HD (NCT04556656), though functional status, not chorea, is the primary outcome.

5.3 Memantine

Memantine is a noncompetitive, low- to medium-affinity antagonist of NMDA glutamate receptors. It is thought to block NMDA receptor-operated ion channels, thus reducing excitotoxic glutamate release. In an open-label study of 9 HD patients, treatment with memantine at 20mg/day resulted in significant improvements in chorea scores form baseline [107].

5.4 Deep brain stimulation

Deep brain stimulation (DBS) has been proposed as a treatment for HD chorea which could address motor symptoms with fewer side effects than pharmacological therapies. With DBS, electrodes are surgically implanted into targeted brain structures and are thought to reduce symptoms through disruption of aberrant circuits. Small studies have reported significant and sustained reductions in chorea after DBS targeting the pallidum [108–111]. One study reported better antichoreatic effects, but worse side effects (e.g. bradykinesia, spasticity), with ventral versus dorsal internal GP (GPi) stimulation [109]. Another small study found that external GP (GPe) stimulation was as effective as GPi stimulation for chorea reduction [111]. Evidence for effects on functional status, cognition, and psychiatric symptoms has been mixed, with most studies reporting no significant effects of GP DBS on these outcomes in HD. DBS has primarily been used in HD patients with refractory chorea, so effects in patients with early-stage disease or with medication-responsive chorea are unknown. Multiple randomized controlled trials are planned or currently underway to investigate the long-term safety and efficacy of DBS in a larger group of HD patients (NCT04244513 and NCT02535884).

5.5 Risk factor modification

Several factors have been identified which have the potential to affect chorea or motor onset in HD. As mentioned above, stimulants may worsen chorea in HD [33, 34]. Similarly, retrospective analyses have linked substance abuse to earlier onset of HD [35, 112], and modification or reduction of substances such as tobacco and alcohol could improve presentation of chorea. It has also been suggested that environmental factors (e.g.

socioeconomic status, exposure to pollutants, diet) may play a role in the age of onset and presentation of HD symptoms [113], though this requires further investigation. Interestingly, higher weight is a predictor for slower disease progression in HD [114], though it is possible that weight loss and motor symptom progression may simply be coexisting byproducts of subcortical atrophy. Finally, exercise interventions have been trialed in persons with HD [115, 116], and some benefits for motor symptoms have been seen [117, 118]. However, to our knowledge, no studies have specifically examined the effects of exercise interventions on chorea in persons with HD. Overall, there may be modifiable risk factors which modulate chorea, but higher-quality evidence is needed to confirm these effects.

6.0 Conclusion

Chorea is a pervasive symptom of HD which has been linked various negative outcomes including loss of independence and poorer quality of life. HD patients, caregivers, and clinicians agree that it is important to treat chorea, but there is not consensus on which medications should be used as first-line therapy. This ambivalence regarding treatment is due primarily to a lack of high-quality evidence comparing efficacy and tolerability of antipsychotics and VMAT-2 inhibitors. Additional factors include international differences in availability of medications as well as patient comorbidities which drive decision-making. Other variables may affect the presentation of chorea, but more research is needed.

7.0 Expert Opinion

A critical gap in our current understanding of treatment for HD is the lack of comparative effectiveness data for available therapies. Although one randomized controlled trial (NCT00632645) compared olanzapine, tetrabenazine, and tiapride, results have yet to be published. Additionally, equipoise for treatment of chorea exists both *between* classes (i.e. deciding between a VMAT-2 inhibitor or antipsychotic) and *within* classes (i.e. which VMAT-2 inhibitor is best; which antipsychotic should be used). Further, dosing decisions are made at an individual level, and can be highly variable. This is especially true for antipsychotics, which are used off-label due to lack specific dosing directions for HD. Clinicians make decisions for treatment, accounting for personal experiences and patient comorbidities, but these individual experiences can lead to extreme variety in treatment practices. Further, because HD is a rare disease, clinicians have fewer experiences from which to derive their decision-making paradigms. Thus, multicenter, prospective data is critical to inform the safest and most effective use of available therapies.

The ultimate goal of future research in this area is to treat chorea with interventions that are safe and tolerable, and optimized at the patient level. Clarification is needed regarding safety and efficacy of individual antipsychotic agents for chorea as well as dual therapy with VMAT-2 inhibitors. Although placebo controlled randomized controlled trials are the gold standard for determining safety and efficacy, high costs and ethical issues related to withholding treatment and stringent exclusion criteria render them impractical in this situation. We believe that prospective observational comparative effectiveness studies are an ideal mechanism for comparing antichoreatic medications, particularly antipsychotics. Comparative effectiveness studies aim to compare risks and benefits of available

interventions in real-world (e.g., clinical) settings through prospectively planned, rigorous statistical analyses [119]. Although there have been several observational registry studies in HD (NCT00313495, NCT01574053, NCT01590589, and NCT00051324 among them), data from these studies cannot satisfactorily address these questions due to infrequency of follow-up visits and lack of pharmacovigilance and dosing information. Indeed, medication management requires close follow-up to assess treatment response within weeks or months, and annual assessments miss intermittent developments seen in clinical practice. Additionally, retrospective analyses using these databases are helpful for hypothesis generation, but such evidence lacks adequate rigor to shift clinical practice paradigms. We propose that prospective observational comparative effectiveness studies, which follow standard clinic schedules in real world HD samples, may provide guidance for better, safer symptom reduction. This may in turn lead to improved functional and quality of life outcomes for HD patients and caregivers, including those typically excluded from clinical trials.

Another outstanding question relates to timing of antichoreatic medication initiation. It is unclear whether antipsychotics or VMAT-2 inhibitors have disease-modifying effects over time, though it is theoretically possible that earlier use of VMAT-2 inhibitors could prevent D2 receptor upregulation and reduce chorea burden as the HD progresses. On the other hand, early use of risperidone, with strong D2 affinity, could lead to faster progression of dystonia and bradykinetic features of HD. Longitudinal comparative effectiveness studies could help answer these outstanding questions as they pertain to real-world HD patients, with consideration for comorbidities requiring treatment (e.g. psychiatric symptoms) or modifying treatment (e.g. anosognosia or dysphagia leading to noncompliance) as well as individual medication histories and financial limitations.

Currently, many potential treatments are under investigation in HD that may have the potential for disease modification by reducing mutant huntingtin protein. These treatments offer the exciting possibility of slowing disease progression in HD. If approved, we believe there will be an influx of HD patients who are seeking care for the first time. The potential for increased functional years in persons with HD is a wonderful possibility that will significantly change the landscape of HD treatment. However, although disease onset may be delayed, persons with HD will still require treatment for symptoms of HD. These treatments will most certainly increase the cost of care for HD and extend both prodromal and symptomatic years of disease. It is now even more vital to compare long-term safety and effectiveness of existing HD therapies.

As new treatment options emerge for HD patients, we are particularly interested in creative solutions for reaching persons outside of traditional specialty clinics. Intrathecal treatments, for example, will require regular lumbar punctures for drug delivery. An unfortunate result of this may be that these therapies are reserved for those living close to academic medical centers or who have the means for frequent travel. This is a phenomenon already seen in clinical trials investigating these drugs, and it presents a dilemma of justice regarding access for rural and lower income patients. A further ethical quandary will emerge regarding age and disease stage of disease modifying treatments, especially given our incomplete understanding of the role of wild type huntingtin and lack of long-term safety data for

huntingin suppression. Considering the field's prioritization of motor symptom control, success of disease modifying therapies will likely be gauged by chorea and other motor outcomes. Even functional status outcomes used in HD (i.e. UHDRS Total Functional Capacity) reflect primarily motor function, and may miss important effects of psychiatric and cognitive symptoms [120]. Thus, we believe that the field should prospectively study differing treatments for chorea, and non-motor comorbidities, to gain evidence-based guidance for individualized care.

List of Abbreviations:

HD	Huntington's disease
VMAT-2	vesicular monoamine transporter type 2
FDA	Food and Drug Administration
US	United States
DBS	deep brain stimulation
CAG	cytosine-adenine-guanine
MSNs	Medium Spiny Neurons
GP	Globus Pallidus
UHDRS-TMS	United Huntington's Disease Rating Scale Total Motor Score
Q-Motor	Quantitative motor
BMI	body mass index
GPi	internal GP
GPe	external GP

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Article Highlights

- VMAT-2 inhibitors are the only medications approved by the FDA to treat HD chorea
- Antipsychotics are commonly used to treat chorea in HD, but there is no consensus on which agents are safest and most effective
- There is little data to support use of other therapies for treatment of HD chorea, though deep brain stimulation (DBS) is a promising option.
- Comparativeness effectiveness studies are needed to determine which agents are safest and most effective for reducing chorea and comorbid HD symptoms (e.g. psychiatric symptoms).
- Now is the ideal time for these studies, as the emergence of possible disease-modifying therapies increases the likelihood that HD patients may live longer, and more patients will seek care in the coming years.

Table 1.

Dosing and Costs of Antipsychotics and VMAT-2 Inhibitors Used to Treat Chorea in the United States

Class	Medication	FDA Indicated for HD chorea?	Adult dosing[1]			Benefit for psychiatric symptoms?	Available generic?	Cost for 30-day supply of lowest target dose[2]
			Initial daily dose	Target daily dose	Divided dose?			
Atypical antipsychotics[3]	risperidone	no	2–3 mg	1–8 mg	yes	yes	yes	$1.50
	olanzapine	no	5–15 mg	5–20 mg	no	yes	yes	$4.50
	aripiprazole	no	10–15 mg	10–15 mg	no	yes	yes	$11.18
	clozapine	no	12.5 mg	300–600 mg	yes	yes	yes	$32.63
	quetiapine	no	25–100 mg	50–800 mg	yes	yes	yes	$7.80
VMAT-2 inhibitors	tetrabenazine	yes	12.5 mg	25–100 mg	yes	no	yes	$430.77
	deutetrabenazine	yes	6 mg	6–48 mg	yes	no	no	$1,916.15
	valbenazine	no	40 mg	80 mg	no	no	no	$6,649.83[5]

[1] Antipsychotic and valbenazine dosing includes monotherapy dose range for all approved indications according; tetrabenazine and deutetrabenazine include only HD approved doses.

[2] Cost estimates are from www.goodrx.com. Costs are lowest listed costs, not accounting for insurance coverage, including available coupons and mail order prices listed on www.goodrx.com as of 10/6/20. For brand name medications, coupons and patient assistance programs typically lower the price, but this is dependent on patient insurance.

[3] First generation antipsychotics and therapies not approved in the US are not included on this list, as we aimed the include the most relevant agents. All antipsychotics listed refer to immediate release oral formulations.

[4] GoodRx pricing was available only for the starting dose pack, not for the 80 mg target dose