Antidopaminergic Medications in Huntington's Disease

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Abstract

Huntington's Disease (HD) is a progressive neurodegenerative disorder marked by motor, cognitive, and behavioral impairments. Antidopaminergic medications (ADMs), such as VMAT2 inhibitors and antipsychotics, are commonly used to manage HD motor disturbances and behavioral disorders. For patients and caregivers, ADMs are an important tool for managing symptoms that negatively affect daily life. However, the impact of ADM use in HD is not firmly understood due to a lack of robust, systematic studies that assessed their overall effect on HD disease. A mounting body of evidence suggests these medications may be associated with worse clinical measures of cognitive function and functional impairment. While regulatory guidelines highlight adverse effects like sedation, cognitive dysfunction, and extrapyramidal symptoms, it is unclear whether ADMs directly impact disease progression or if the side effects mimic or exacerbate measures of HD symptoms in clinical trials. Given ADM effects on the central nervous system and biological uncertainty within HD outcomes, clinical trial designs should recognize the impact of ADMs on key outcomes, as measured by acceptable scales including Total Functional Capacity (TFC), Stoop Word Reading (SWR), Symbol Digit Modality Test (SMDT) and the composite UHDRS (cUHDRS). The development of novel HD interventions requires consideration of concomitant ADM use that may influence measures of disease presentation. In this review, we highlight the role of ADMs in HD management, their symptomatic benefits and potential risks, especially with high dose associated side effects, interactions with CYP2D6 inhibitors, and the individualized need for careful dose monitoring for clinical care and trial design.

Introduction

Huntington's Disease (HD) is the most common autosomal dominant neurodegenerative disorder, affecting approximately 10-12 people per 100,000 globally (1). HD is characterized by a progressive worsening of motor, cognitive, and behavioral symptoms, which inevitably leads to the loss of independence and eventual mortality expected within 15-20 years from clinical diagnosis (2). Unfortunately, current HD treatments are palliative only, designed to manage the spectrum of symptoms that emerge from disease onset. While expanded CAG repeat mutation in the Huntingtin gene (HTT) and an individual's age are the most reliable biological predictors for assessing HD risk and disease severity, the underlying etiological mechanisms that drive the disease are not firmly understood. Nonetheless, for decades, an important tool in HD symptom management has been the use of antidopaminergic medications (ADMs), which include regulatory-approved VMAT2 inhibitors and the off-label use of antipsychotic medications (e.g., neuroleptics).

These drugs are primarily aimed at managing the motor symptoms associated with HD, such as chorea, as well as behavioral disturbances (3,4). For many patients and caregivers, by targeting abnormal HD dopaminergic activity, these medications provide symptomatic relief for patients and serve as a key resource for caregivers in managing symptoms. However, despite the frequent and widespread use of ADMs, a growing body of literature continues to underscore the risk that ongoing ADM use may complicate HD progression. Given the broad action of ADMs in the central nervous system (CNS) and their sensitive drug metabolic profile–particularly concerning interactions with CYP2D6 inhibitors (5)–there is a need for continued awareness and careful consideration in ADM use for HD treatment.

In this review, we will focus on the important role of ADM use in HD management, assessing their impact on clinical measures and outcomes. We also examine the effects of ADMs on patients, including both their clinical benefits and the significant risks associated with long-term use. Certainly, for clinical studies assessing novel HD

therapeutics, ADMs may influence measures of function and cognition, e.g., total functional capacity (TFC), composite Unified Huntington's Disease Rating Scale (cUHDRS), as well as cognitive endpoints. Thus, we will also explore the implication of ADM interactions with CYP2D6 inhibitors, emphasizing the need for careful dosing and monitoring, particularly in the context of new clinical trials and individualized patient care strategies.

Huntington's Disease: Understanding Natural Progression

Understanding how Huntington's Disease (HD) progresses is crucial for interpreting the outcome measures commonly used in clinical trials and the studies discussed in this review. HD follows a predictable progression through a series of stages, clinically operationalized based on total functional capacity (TFC) outcome measures (6,7). In HD staging, a decline in TFC correlates with a decline in overall function and independence, with scores 0 to 13. Higher TFC scores indicate better overall function and independence, e.g., Stage I or TFC 11-13; whereas lower scores indicate more severe impairment with advanced HD disease (7). As a measure of "real-world" function within the Unified Huntington's Disease Rating Scale (UHDRS), the TFC measures how well an individual manages to live independently across five domains: occupation, finances, domestic chores, self-care (e.g., personal hygiene), and level of assistance required in daily life (7,8). Importantly, the TFC score is widely used in clinical trials to evaluate progression of a patient's disease stage and function (7,8).

The natural progression of manifest HD using the declining rate of TFC score has been well characterized (7,9). In a large cohort, multi-national, prospective longitudinal study across Australia, Canada, and the United States, the estimated annual rate of TFC decline ranged from 0.4 to 0.8 points lost per year (10). Importantly, the natural rate of HD progression is non-linear: As HD disease progresses to more severe stages, *the annualized rate of TFC decline decreases* (7). For example, Marder and colleagues showed an annual TFC decline of 0.97 for stage I/II, 0.38 for stage III, and 0.06

for stage IV/V (7). Thus, as HD progresses, TFC scoring becomes less sensitive to detecting symptomatic changes in later stages ("floor effect") and in early, premanifest or prodromal phases when symptoms are minimal or undetectable (a "ceiling effect") (7,11,12).

Indeed, there have been significant efforts to improve upon existing outcome assessments for HD progression, while also incorporating recent staging tools, such as the Huntington's Disease Integrated Staging System (HD-ISS), to better classify disease stages (13). Additionally, some putative biomarkers, such as neurofilament light (NfL) chain expression, have been studied (14,15), but they have not yet been fully validated, adopted into clinical use, or achieved universal consensus within the HD community. The development of the cUHDRS, which combines the weighted sum of an individual's total motor score (TMS), cognitive assessments (Stroop Word Reading, SWR, and Symbol Digit Modalities Test, SDMT), and TFC, offers a more sensitive measure for monitoring overall HD progression, and overcoming the "ceiling effect" limitations with TFC staging (16–18).

Antidopaminergic Medications in HD

Current strategies for the treatment of HD focus on symptom management, only, as no approved therapeutic intervention has been shown to limit or slow disease progression. Because HD symptoms are heterogeneous, may vary in severity over time, and worsened by a host of factors, including stress, fatigue, and other associated disorders, e.g., anxiety, depression, and other behavioral disturbances, it is important to note that any of these aspects be addressed alongside the use of any pharmacotherapy in managing HD symptoms (19).

The most visible and recognizable symptoms in HD are the broad spectrum of motor manifestations. In fact, although cognitive and behavioral symptoms often emerge prior to manifest HD, a diagnosis which

is based on the presence of characteristic (i.e., significant) motor symptoms for HD, the only regulatory-approved drugs for HD are vesicular monoamine transporter 2 (VMAT2) inhibitors: tetrabenazine (Xenazine), deutetrabenazine (Austedo), and valbenazine (Ingrezza) (see **Table 1**). These drugs are indicated to treat motor symptoms in HD, i.e., chorea. Although other medications are used in HD management, including a host of antipsychotics (e.g., dopamine receptor antagonists), these drugs are not approved for any HD indication and are used off-label to manage behavioral aspects of the disease. For example, despite a pressing need for additional scientific proof for their efficacy (23–25), antipsychotics have been prescribed to address a broad range of issues such as agitation, aggression, psychosis, and other behavioral disturbances commonly observed in HD patients (26).

Certainly, in clinical practice, using current outcome assessments for monitoring HD progression can present challenges with interpreting the impact of therapeutic interventions, especially with ADM use. For example, the package insert for AUSTEDO (deutetrabenazine)—a clinically FDA approved VMAT2 inhibitor for chorea—explicitly states that "[p]rescribers should periodically re-evaluate the need for AUSTEDO in their patients… [as it] may be difficult to distinguish between adverse reactions [of the drug] and progression of the underlying disease." (*package insert, sections 5.1 and 5.5* (27)). Similarly, UK and US (FDA) regulatory labeling for XENAZINE (tetrabenazine) also underscores the difficulties clinicians face "…distinguishing between adverse reaction and progression of the underlying HD disease." (*package insert, section 5.2 (28,29)*), which may be particularly challenging in more advanced stages of the disease when ADMs are more commonly prescribed (30,31). Moreover, the negative impact of ADMs on measures of cognitive endpoints also requires notice in regard to potential challenges with clinical care. The SWR and SDMT, two subdomain measures within the cUHDRS, are important assessments for cognitive function in HD and are highly sensitive to ADM use (32,33).

Antipsychotics, for example, are commonly associated with powerful sedation or somnolence, side effects that can confound performance in these cognitive measures and complicate cUHDRS scoring (34). This emphasizes the broad challenges in assessing cognitive performance in patients using ADMs and highlights the limitations of current outcome assessments across the spectrum of HD symptomology.

Clinical Guidelines for ADM Use in HD

The biological effects of ADMs in the CNS still requires investigation. The mechanism of action of all ADMs is generally believed to modify pathological dopamine signaling associated with HD, but the exact biology driving ADM efficacy is not firmly understood (35,36). This is particularly relevant and concerning given the wide prevalence of ADM use in HD patients. Nearly 30-50% of patients with manifest HD are prescribed at least one ADM (3,4,30,37–44) and, importantly, by latter stages of HD, a greater proportion of HD patients receive ADMs with up to 58.9% of patients receiving more than one ADM. Based on an analysis of the Enroll-HD cohort (3), more than 37% of HD individuals taking ADMs in this observational cohort study received ≥2 ADMs (3). It can be inferred that many HD patients in advanced stages of the disease who received multiple ADMs, e.g., combined a VMAT2 inhibitor with an antipsychotic. Given the prevalence and widespread of ADM use in the management of HD, it is prudent to understand the risks and uncertainty of these drugs in those individuals who use them.

Currently, tetrabenazine, deutetrabenazine, and valbenazine are the only regulatory-approved treatments for chorea in HD in both the US and Europe. As VMAT2 inhibitors, they are thought to counteract the "hyper dopaminergic" state present in HD (35). Valbenazine, recently approved in the US, is indicated for the treatment of tardive dyskinesia and chorea associated with HD (45,46). Although tardive dyskinesia is not necessarily a direct symptom of HD, it is a motor condition that may arise with long-

term off-label antipsychotic use in HD (46). VMAT2 inhibitors serve to deplete presynaptic dopamine, and mechanistically function similar to dopamine antagonists. Taken together, tetrabenazine, deutetrabenazine, and valbenazine continue to be important regulatory approved tools in HD anti-chorea treatment and have demonstrated efficacy on management of chorea in high-quality randomized controlled trials (RCTs) (45,47–49).

However, there is still a large unmet need for therapies that can meaningfully impact the course of HD across the range of other symptoms associated with the disease (22,50). Despite scientific and clinical data supporting the beneficial effects of VMAT2 inhibitors for chorea, RCTs and open label extension studies for tetrabenazine and deutetrabenazine also revealed deleterious effects of these drugs on aspects of cognition and other domains of function, as well as associations with depression and anxiety (47,48,51,52). There are no prospective placebo controlled RCTs that assess or demonstrate efficacy of VMAT2 inhibitors for improving cognition, functional capacity, or behavioral symptoms in HD.

Moreover, there is presently insufficient evidence to support the safety and efficacy of antipsychotic use in any indication associated with HD. Based on a comprehensive evidenced based review (53), no clinically available antipsychotics have shown efficacy for addressing chorea according to current best evidence-based medicine standards, i.e., RCTs (level Ia trials). While a few antipsychotics have been studied in non-randomized controlled trials (level Ib trials), they have produced conflicting results, e.g., positive and negative findings, depending on measured outcome (19,41). This may be due in part to the less-rigorous nature of these study designs or dosing regimens, diversity of patient populations, or the lack of statistical power. In general, there is still insufficient evidence for the treatment of non-chorea symptoms such as psychiatric disturbances or dementia using any antipsychotics in HD. As such, no

clinical approval, guidance, or recommendations have been granted regarding the use of antipsychotics in HD (22,23,53). Certainly, it should be acknowledged that antipsychotics are a stopgap measure for addressing non-motor symptoms, even though their impact in HD remain under-studied. Taken together, despite the limited benefits of existing ADMs for a chorea, and the continued off-label use of antipsychotics for managing other symptoms of HD, there is a clear need to be aware of the lack of data supporting the use of ADMs outside of their limited indication for chorea, and the potential risk for ADM-induced adverse events. Emerging evidence, as discussed below, also suggests a potential risk of ADMs worsening measures of the symptomatic profile in HD (23,24,53).

Safety Uncertainties of VMAT2 Inhibitors and Antipsychotics in HD

VMAT2 inhibitors

The primary benefit of VMAT2 inhibitors lies in their ability to significantly reduce chorea. Nonetheless, all ADMs exhibit dose-dependent side effects, some serious and can be difficult to distinguish from natural HD disease progression (*package Insert, section 5.1 & 5.5* (27)). Regulatory labels for VMAT2 inhibitors, such as deutetrabenazine and tetrabenazine, provide clear warnings into their safety profiles and indicated use in managing chorea in HD. For example, FDA regulatory labeling for Austedo (deutetrabenazine) states that the drug "…may cause a worsening in mood, cognition, rigidity, and functional capacity—" (*package insert section 5.6 (27)*). Xenazine (tetrabenazine) regulatory labeling similarly states that evidence from a 12-week controlled trial that "…[the drug] was shown to cause a slight worsening in cognition…", with "[s]edation as the most common dose-limiting adverse reaction." (*package insert section 5.2 and 5.7 (54)*). In the longer open-label studies, 48 and 80 weeks, somnolence occurred in up to "…57% of XENAZINE-treated patients," and drug labeling further cautions prescribers and patients to know how the drug affects the patient once a maintenance dose is reached (*package insert* section 5.7 (54)).

The more recently approved Ingrezza (valbenazine) carries similar regulatory labels, underscoring concerns with VMAT2 inhibitors. The boxed warning states that the drug "[i]ncreases the risk of depression and suicidal thoughts and behavior in patients with Huntington's disease" (*package insert, section 5.1 (25)*). In agreement with labeling for tetrabenazine and deutetrabenazine, there are also labels warning that somnolence and sedation with valbenazine may "…impair a patient's ability to drive or operate hazardous machinery" (*package insert, section 5.6 (25)*). Notably, with valbenazine, in three placebo-controlled studies on tardive dyskinesia, 3% of patients treated with the drug experienced Parkinson-like side effects, e.g., "difficulty moving or loss of ability to move muscles voluntarily, tremor, gait disturbances, or drooling", compared to less than 1% in the placebo group. This is particularly important for HD, as drug-induced parkinsonism has the potential to cause more functional disability than untreated chorea for some HD patients (25). Taken together, VMAT2 inhibitors can offer tangible benefits, especially where managing chorea in early-manifest stages of HD can contribute beneficially to a patient's independence and quality of life. Yet there is still much uncertainty with these class of approved drugs, and therefore dosing strategies in HD management should be carefully tailored for each patient to balance benefits with potential risks.

Antipsychotic Medications

Antipsychotic medications are not approved by any regulatory body for any indications associated with HD. However, they are often prescribed off-label to manage a range of HD symptoms. Specifically, nearly 70% of antipsychotic prescriptions for HD are used for managing chorea (3,4,42,44). Additionally, antipsychotics are prescribed for 20-30% of patients with HD to address behavioral disturbances and psychiatric symptoms, such as aggression and irritability. A large cross-sectional analysis of the international Enroll-HD dataset found that the use of antipsychotics tends to rise in

advanced stages of the disease, likely due to more frequent behavioral symptoms—The mean number of antipsychotic prescriptions per stage I HD patient was 0.16 versus 0.68 for stage IV disease (30,47,55). Until now, there is no formal guidance or clinical recommendation in their use for HD treatment. This issue is further emphasized by numerous regulatory labels that outline antipsychotics' adverse event profiles.

Food and Drug Administration (FDA) and European Medicines Agency (EMA) labels for antipsychotic s specifically highlight a wide range of adverse events that negatively impact cognition and function in HD (i.e., confusion, amnesia, dizziness, somnolence, amotivation, mood changes, and motor EPSEs). Among common side effects, somnolence is particularly notable with antipsychotic s that antagonize the 5-HT2A receptor (see **Table 1**), a serotonin receptor involved in cognition and sleep-wake regulation. Antagonism of this receptor can disrupt normal serotonin function, contributing to drowsiness and potentially compounding cognitive decline in HD (56). More broadly, FDA labels demonstrate that functionally impairing adverse events in placebo controlled trials are 2-3x higher in antipsychotic-treated patients relative to placebo (34). Labels for olanzapine risperidone, quetiapine, haloperidol, and aripiprazole all caution on the potential of the antipsychotic drug class to cause cognitive impairment and drowsiness, highlighting the direct adverse impact this has on functioning (e.g., operating machinery). The risperidone label, for example, states that it "…has the potential to impair judgement, thinking, and motor skills…" and that patients should be cautioned about risperidone until they are reasonably certain that the therapy does not affect them adversely (*package insert section* 5.9 (54)). Likewise, aripiprazole "…may cause somnolence"—and when combined with potential extrapyramidal side effects (EPSEs), such as motor and sensory disruptions, this could lead to fall-related injuries (*package insert section 5.8 (57)*). Somnolence indeed may be a major driver of these warnings and HD

patients experience this side-effect frequently with second-generation (atypical) antipsychotics, e.g., neuroleptics, such as olanzapine and risperidone (15-35% versus placebo rates of 5-15%) (58,59). Explicit labels for both risperidone and clozapine labels highlight specific warnings with somnolence (54,60) and with dose-related somnolence in "…41% of high-dose risperidone treated patients reported…compared with 16% of placebo patients" (*package insert, section 5.9 (54))*. EPSEs, e.g., tremors, rigidity, bradykinesia, akathisia, dystonia, are not far behind with occurrence rates ranging from 5-15% versus 0-5% in placebo groups (61,62). Prevalence estimates taken from trials in adult psychiatric populations (schizophrenia) are expected to be even greater in older populations, patients with neurodegenerative disorders, and patients taking concomitant VMAT2 inhibitors (63).

It is also important to note that regulatory guidelines caution against using antipsychotics in neurodegenerative conditions like Alzheimer's Disease and Lewy Body Dementia, which affect brain regions similar to those impacted in HD (23). Current clinical guidance cautions strongly against the routine or long-term use of antipsychotics for the treatment of behavioral disturbances in patients with dementia (33,55). The Maudsley Prescribe Guidelines in Psychiatry is clear that antipsychotics "…should not be used routinely to treat agitation and aggression in people with dementia." (20). Certainly, specifically regulatory labeling by the FDA for risperidone highlight that "[p]atients with Parkinson's Disease or Dementia with Lewy Bodies who receive antipsychotics…are reported to have an increased sensitivity to antipsychotic medications" (*package insert, section 5.16 (54))*. Such increased sensitivity to antipsychotics presented as postural instability with frequent falls, EPSEs, and clinical features consistent with NMS. In EMA labeling, "…confusion [and] obtundation…" are also reported in patients with these other neurodegenerative diseases taking antipsychotic medications (*package insert (64))*. Such warnings are relevant for HD given the overlapping neurodegenerative

processes and brain regions involved, suggesting that HD patients might also be at heightened risk of functional impairment from antipsychotic adverse effects. Underscoring this, a long-term study of patients with schizophrenia showed an association of brain volume atrophy with long-term antipsychotic use. Here patients underwent repeated MRI neuroimaging soon after psychotic symptom onset (average 3 scans) over 7.2 years (max 14 years). As compared with modest associations of psychotic illness on brain volume loss, antipsychotic treatment (mean daily dose) was associated with significantly smaller brain tissue volumes and larger CSF fluid volumes. Statistical models in this study controlled for alcohol, illicit drug use, illness severity, and follow-up duration (65). It should be noted that even in healthy individuals, a single dose of sulpiride or other antipsychotic use has been shown to negatively impact cognition, leading to cognitive impairments (66–68).

The well-documented risk of EPSEs associated with antipsychotic use is dose-dependent and directly linked with their level of dopamine D2 receptor antagonism (69,70). Although antipsychotic-induced antagonism of dopamine D2 receptors in the mesolimbic pathway can alleviate psychosis, non-selective binding in the nigrostriatal pathway can lead to emergent EPSEs, such as akathisia, dystonia, and parkinsonism. The risk and severity of EPSEs increases with higher drug exposure, especially when drug-to-receptor occupancy exceeds 75-85% (69). This dueling drug effect creates a therapeutic challenge in clinical care: Increasing antipsychotic dosing may seem intuitive to manage psychosis, but it can inadvertently worsen measures of motor symptoms. There is also a risk of a "masking effect" where antipsychotics suppress involuntary movement associated with psychosis, but simultaneously worsen the readout of other motor symptoms. This masking can complicate the true clinical landscape, making it difficult to assess disease progression and treatment efficacy. Thus, careful dose management is crucial to avoid crossing the critical D2 receptor occupancy threshold, which could further worsen

EPSEs rather than alleviate the behavioral symptoms (69). As shown in **Table 2**, antipsychotic D2 receptor antagonists vary in their affinity and potency. High-affinity and highly potent antipsychotics, such as risperidone and olanzapine, block D2 but contribute to significant risk for side effects, including impaired cognition, parkinsonism, and EPSEs (71–73). In contrast, low-affinity/low-potency blockers of D2 receptors including tiapride, aripiprazole, or quetiapine may have lower risk for side effects (74–76). Aripiprazole, in particular, is noteworthy for its multi-faceted mechanism-of-action as a partial dopamine D2 and 5-HT1A receptor agonist, as well as a serotonergic 5-HT2A receptor antagonist (70,74) (see **Table 1**). This unique mechanistic profile allows aripiprazole and other partial D2 agonists to stabilize dopamine activity and provide therapeutic benefits without fully blocking D2 receptor function, thereby reducing EPSE risk even at higher receptor occupancies (69).

Impact of Combining VMAT2 Inhibitors and Antipsychotics

Combining VMAT2 inhibitors with a antipsychotic may present compounding risks. Labels for tetrabenazine and deutrabenazine caution against their use with concomitant antipsychotics, in part due to their exacerbating risks for EPSEs and fatal antipsychotic malignant syndrome (NMS), a rare but serious reaction characterized by high fever, muscle rigidity, and altered mental status, and QTc prolongation (27,28,77,78). For tetrabenazine, FDA labels state that "[t]he risk for Parkinsonism, NMS, and akathisia may be increased by concomitant use of XENAZINE (tetrabenazine) and dopamine antagonists or antipsychotics (e.g., chlorpromazine, haloperidol, olanzpine, risperidone, thioridazine, ziprasidone)" (*package insert, section 5.4, 5.5, 7.6 (28)*). This is in agreement with the UK-specific label for tetrabenazine, "[i]t is not recommended to use this medicine with… antipsychotics." (UK *package insert section 2 (79)*).

CYP2D6 Metabolism: Pharmacokinetic Considerations for ADM Dosing, Utility, and Safety

There are no contraindications for using anti-dopaminergic medications (ADMs) with or without CYP2D6 inhibitors. However, the combination may increase the risk of complications, necessitating close dose monitoring and dose-adjustments to manage potential side effects. The substantial side effects associated with ADM use in HD, especially at higher doses as highlighted by regulatory labels, strongly supports the need for continued caution due to the risks for EPSEs, parkinsonism, and other adverse events. ADM efficacy and safety is dose-dependent (20,80), and further affected by pharmacokinetic factors, including drug-interactions and individual patient metabolic factors. A key pharmacokinetic consideration in ADM impact in HD is the role of CYP2D6, an enzyme in the liver that is crucial for metabolizing many ADMs, including VMAT2 inhibitors and a broad range of antipsychotics (81) (see **Table 3**).

Concomitant use of CYP2D6 inhibitors with these medications, e.g., tetrabenazine, deutetrabenazine, risperidone, would result in clinically significant increases in ADM plasma concentrations and potentially increase the risk for adverse effects. Underscoring this point, ADM regulatory labels provide clear recommendations to monitor dosage and lowering doses of ADMs when administered along with CYP2D6 inhibitors (82–85). For tetrabenazine, FDA regulatory labeling for example explicitly states that "…a maximum single dose should not exceed 25 mg if administered in conjunction with a strong CYP2D6 inhibitor." (*package insert, section 7.1 (28)*). Warnings for deutetrabenazine also state that the "[m]aximum recommended dose of AUSTEDO is 36 mg per day (18 mg twice daily)." (*package insert section 7.1 (27)*). Along with pharmacokinetic considerations and drug interactions for VMAT2 inhibitors, many antipsychotics may also require dose adjustments and increased monitoring when co-administered with CYP2D6 inhibitors, as these interactions can lead to increased drug levels,

accompanying side effects, and potentially more progressive symptoms, especially in patients who identified as poor metabolizers. Aripiprazole labeling, for example, states that a dose reduction is recommended for patients who are co-administered a strong CYP2D6 inhibitor or are CYP2D6 poor metabolizers (*package insert, section 2.4 (57)*). Taken together, ADM treatment-emergent events due in part to variability in CYP2D6 activity, i.e., poor metabolizers or those on strong inhibitors, can lead to higher drug levels and increased risk of side effects. Regulatory guidance for ADMs in general highlights the need for careful dose monitoring to manage pharmacokinetic risks, particularly with high-dose ADM use.

ADM Overall Impact in HD Progression

In agreement with the well-documented adverse events for ADMs, there is a mounting body of published evidence that show that ADM use in HD patients is associated with greater incidence of cognitive and functional impairments, as well as faster disease progression compared with patients not prescribed ADMs. Strong evidence for the impact of ADM on HD emerge from large prospective longitudinal cohort studies, spanning US and Europe, i.e., ENROLL-HD, REGISTRY, TRACK-HD, and COHORT, which have consistently shown significant and clinically meaningful associations between ADM use and worsening clinical measures of cognition and functional capacity (3,4,38,42,86–88) (**Table 4**; also see **Supplemental Figure 1**).

In both the pivotal, randomized placebo-controlled Phase 3 trial of tetrabenazine as an anti-chorea treatment for HD (47), and the open-label follow up study (51), there was significantly worse functional and cognitive outcomes in patients randomized to tetrabenazine. Specifically, in the RCT for tetrabenazine as antichorea therapy (47), tetrabenazine-treated patients exhibited significant functional decline (UHDRS-Functional Assessment (FA) [mean $\pm$ SE]: -0.8 $\pm$ 0.3 vs +0.4 $\pm$ 0.4 in placebo, Δ vs

placebo -1.2, p=0.02) and worse cognitive performance (SWR: -4.8 ± 1.5 vs +1.8 ± 2.1 in placebo, Δ vs placebo -6.6, p=0.01). As noted earlier, these observations resulted in regulatory labeling regarding the potential worsening of these symptoms with tetrabenazine use in HD. In agreement, Tedroff and colleagues (4) also reported evidence demonstrating the negative impact of ADMs in HD progression from an analysis of 651 patients in the European REGISTRY cohort (n=320 treated with antipsychotic s or tetrabenazine versus n=331 ADM-naïve). Here ADM use was associated with accelerated functional decline across TFC, Functional Assessment, and Independence Scale (IS) outcome scores (annualized progression rate in TFC: -1.1 vs -0.7 units/year, p<0.01; FA: -2.0 vs -1.1, p<0.001; IS: -5.7 vs -3.7, p<0.001). Note that at baseline, patients receiving ADMs—for chorea or behavioral disturbances, 70% and 18%, respectively—started with significantly worse total motor scores (TMS: 41.7 vs. 26.6; p<0.001) and lower total functional capacity (TFC: 7.1 vs. 9.7; p<0.001). Because progression rates in more advanced stages of HD are slower, e.g., floor effect, the decline in progression rates in this longitudinal analysis are unlikely to be solely due to baseline differences in patient functional capacity or symptom severity. Thus, the authors suggested that ADM treatment was associated with more advanced and rapidly progressing HD.

In agreement, additional recent evidence from two studies that analyzed data from the Enroll-HD study provide further support that ADM use worsens HD symptom progression (3). In the first study, authors categorized HD patients into ADM or non-ADM groups which were then propensity scored matched for CAG repeat number, age, baseline TFC, and time since diagnosis (**Supplemental Table 2**). Commonly prescribed ADMs in this analysis included tetrabenazine (40.3%), olanzapine (33.5%), and risperidone (21.0%), primarily prescribed for chorea (67%) and behavioral symptoms (28%). Overall findings here showed that despite matching, ADM use was associated with more rapid functional (TFC: -1.0 vs -0.5,

p<0.001; UHDRS Independence Scale: -3.8 vs -2.5, p=0.004) and cognitive decline (composite cognitive z-score: -0.8 vs +0.8, p<0.001). Regression analysis confirmed that ADM use as an independent risk factor for cognitive decline (p<0.0001) (**Figure 1**). Although ADM treatment appeared to slow chorea progression (UHDRS total chorea score: -0.1 vs +0.4, p=0.004), ADM use was associated with worsening dysarthria (p=0.02) and motor coordination (Luria tri-step score, p=0.002). Behavioral outcomes indicated slower progression in irritability (p=0.003) with no significant effects on apathy or depression.

In the second study, Harris et al., analyzed a "pseudo-prospective" cohort of HD patients who initiated ADMs during a follow-up study, as compared with a matched control who did not start using ADMs (3). Although patients who initiated ADM showed no difference in the rate of functional decline before or after ADM initiation (TFC: -0.9 vs -1.0, p=0.66; Independence Scale: -5.2 vs -3.6, p=0.18), treatment with ADM was associated with increased cognitive decline that did not occur in the control (non-ADM) group (p<0.001). Similar to the first study, annualized chorea progression decreased significantly in the period after ADM initiation, as compared before initiation (pre-ADM: 1.1 vs post-ADM: -0.5, p=0.036). Behavioral outcomes indicated no significant changes in depression or apathy, although there was a trend for reduced irritability after ADM initiation (p=0.065). Taken together, the analyses from the Enroll-HD study showed that HD patients taking ADMs experienced faster decline in measures of cognitive function and overall functional capacity as compared with non-ADM users. A secondary analysis confirmed worsening in measures of cognitive symptoms after initiating ADMs, which was not seen in matched controls. While ADMs may help with chorea and irritability, they are linked to measures of worsening cognitive function (e.g., Stroop Word Reading, Symbol Digit Modalities Test),

functional capacity (e.g., UHDRS Total Functional Capacity score, UHDRS Independence Scale), and motor coordination (e.g., UHDRS Luria tri-step task performance).

In a modern, cross-validated machine learning analytic approach of the Enroll-HD dataset, Ghazaleh and colleagues (86) assessed the predictive power of 102 baseline patient variables to assess their ability to predict HD annualized progression in a number of outcome measures. Note that the advantage of a random forest regression model to assess the Enroll-HD dataset is that it automatically accounted for the influence of other baseline predictors (89)—in other words, if one variable, such as cognitive impairment, strongly influenced HD progression rate, the model would recognize this and adjust its predictions accordingly without overestimating the effect of other correlated factors. Taking this into account, although *all patients* in the study showed a decline in cUHDRS, those taking antipsychotics showed a significantly greater decline in cUHDRS score over two years (p<0.001). Overall, findings from this study showed that ADM use (i.e., tetrabenazine and antipsychotics) were consistently in the top 10 predictors for exacerbating measures of cognitive, functional, and cUHDRS outcome.

Along with longitudinal cohort studies (see **Supplemental Table 1**), cross-sectional studies also provide corroborative evidence showing an association between ADM use and their impact on HD progression. In the largest of these studies, Orth et al. (2016) showed evidence of an association between ADMs as well as anti-parkinsonian medications (termed "anti-dyskinetics") on various clinical outcomes in 8,883 pre-manifest and manifest HD patients from two large cohort datasets collected from patients from different geographical locations, REGISTRY (Europe) and COHORT (North America) (38). Note that only 0.7-1.1% of premanifest patients were prescribed these medications. With controls for various patient factors such as disease burden, HD stage, and anti-depressant use, the study revealed a

significant association between ADM prescription and anti-parkinsonian medication with worse functional outcome. Lower independence scores (regression coefficient: B=-0.02, P<0.0001), worse cognitive performance (SDMT: B=-1.78, P<0.0001; word reading: B=-1.75, P=0.015; Stroop interference: B=-1.03, P=0.012), as well as lower total motor scores (TMS: B=2.26, P<0.0001) accompanied ADM use as compared with patients not on these medications. There was no difference in verbal fluency or color naming. Collectively, although cross-sectional and longitudinal studies cannot infer causality, there is broad and convergent evidence, fully aligned with regulatory warnings, that point to ADM use in HD as associated with measures of worsening cognitive and functional outcomes.

Future Perspectives and Conclusion

ADMs are important for management of HD, primarily aimed at controlling motor symptoms such as chorea and behavioral symptoms. By targeting disrupted dopaminergic signaling in HD, these medications continue to be an important, albeit limited, symptomatic management tool for patients, caregivers, and clinicians. However, ADMs have significant side effects which can have an impact on measures of disease progression, impair cognition, and severely disrupt quality-of-life; for example, somnolence and sedation are common side effects of antipsychotics (4,86). These issues create ongoing challenges for effective disease management. Of notable concern is the lack of clear data regarding the long-term use of ADMs in HD, as well as the risk for high-dose ADM associated side effects, especially when these drugs are combined with other drugs, such as CYP2D6 inhibitors. In these cases, clear regulatory labels recommend dose monitoring along with the possible need for dose-reduction to treat behavioral disorders and chorea to minimize the risk of side effects of these drugs. Clinicians should aim to prioritize second-generation medications antipsychotics, e.g., antipsychotics, and reduce doses whenever possible. Consider tapering off medication, if clinically appropriate, particularly for stable patients or when side effects outweigh therapeutics benefits.

For clinical trials, recognizing that ADMs may affect cognition and may be associated with measures of worsening disease outcomes—as measured by TFC, cUHDRS, and various cognitive endpoints—strongly supports the rationale for balanced randomization of patients regarding the use of ADMs at baseline and/or a statistical plan that looks at outcomes with and without ADMs. The potential deleterious effects of ADMs on measures of HD progression and symptom severity could mask clinically meaningful effects of novel medicinal agents, particularly with respect to functional endpoints, which are most relevant to patients. Therefore, it is prudent to ensure that outcome endpoints are analyzed with and without the superimposed effects of ADMs to assess the efficacy of new treatments. Alongside efforts to develop new, effective, and safe medicines for slowing or stopping HD progression, there is a continuing need to develop more reliable and sensitive disease-staging systems, validation of molecular/genomic biomarkers, and encouraging systematic study of the negative effects of ADMs on HD symptoms and disease progression.

Figures Legends

Table 1. Pharmacological agents commonly used in Huntington's Disease (HD), categorized by their mechanism of action (MOA) and clinical application. The primary treatments for HD symptoms include VMAT2 inhibitors to reduce chorea, alongside the off-label use of both typical and atypical antipsychotics, e.g., neuroleptics, to manage psychiatric disturbances, such as irritability and psychosis. Approval locations vary by medication.

Table 2. Antipsychotics with varying affinities and potencies for D2 receptors, highlighting their antagonist or partial agonist properties and potential dose-dependent side effects. Data adapted from (54,57,72–76,90–94)

Table 3. Antidopaminergic medications and their metabolism by CYP2D6. Includes whether ADM metabolites are active, expected drug exposure changes following CYP2D6 inhibition, and key highlights from drug regulatory labels. Data from (27–29,53,95–97)

Table 4. Summary of key interventional and observational studies suggesting that the use of antidopaminergic medications (ADMs) contributes to worsening outcomes in Huntington's Disease (HD), particularly across functional and cognitive domains. These studies indicate a decline in clinical measures, including functional capacity and cognitive performance, in patients using ADMs such as VMAT2 inhibitors (e.g., tetrabenazine) or antipsychotics. Data adapted from Data adapted from (3,4,51).

Figure 1. Annual change in clinical outcome measures in patients with or without antidopaminergic medications (ADMs). Average annual change in (A) UHDRS Total Motor Score (TMS), (B) UHDRS total chorea score, (C) Problem Behaviors Assessment (PBA) irritability score (higher scores indicate worsening), and (D) composite cognitive score (lower scores indicate worsening) in ADM users (n = 466) vs. non-users (n = 466). Groups were matched for age, CAG repeat length, Total Functional Capacity (TFC), and time since diagnosis. Mean ± SE are shown. Significance levels: ***P < 0.001, *P < 0.05 (univariate ANOVA, with change in score as the dependent variable, ADMs as the independent variable, controlling for age, CAG repeat, and gender). Data adapted from (3).

Supplemental Table 1. Summary of observational studies examining the effects of antidopaminergic medications (ADMs) on functional, cognitive, motor, and behavioral outcomes in patients with HD. Five studies using data from the REGISTRY, Enroll-HD, and Huntington French Speaking Network datasets assessed longitudinal changes in HD patients on ADMs compared to untreated controls. Across studies, ADMs were consistently associated with faster rates of functional and cognitive decline. However, ADMs were linked to slower progression in chorea, particularly in early-stage HD, and a reduction in irritability symptoms. Motor outcomes varied, with some studies reporting worsened dystonia but no significant differences in chorea progression compared to non-ADM users. Behavioral symptom progression was comparable between groups, except for reduced irritability in ADM-treated patients. These findings highlight the complex and variable effects of ADMs on HD progression, warranting further investigation into their long-term clinical impacts. Data from (3,4,44,86).

Supplemental Table 2. Baseline characteristics of patients not taking ADMs and taking ADMs, from an observational study of ADMs on HD progression rates using the Enroll-HD cohort. Patients taking ADMs for the study duration, and a control group of patients not taking ADMs (propensity matched for CAG repeat, age, TFC). Data adapted from (3).

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Table 1. Pharmacological agents commonly used in Huntington's Disease (HD), categorized by their mechanism of action (MOA)

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Table 1. Pharmacological agents commonly used in Huntington's Disease (HD), categorized by their mechanism of action (MOA) and clinical application.

Category	Drug	Target/MOA	Clinical Application in HD	Current Approval Location
Anti-Chorea (VMAT2 Inhibitors)	Tetrabenazine	VMAT2 Inhibitor	Reduces chorea by decreasing dopamine activity	US, Canada, Europe
	Deutrabenazine	VMAT2 Inhibitor	Reduces chorea similar to tetrabenazine but with a longer half-life, and potentially more favorable side effect profile	US and Europe
	Valbenazine	VMAT2 Inhibitor	May have potentially fewer side effects than tetrabenazine, and primarily indicated for tardive dyskinesia and efficacy in chorea	US
Neuroleptics (Atypical)	Olanzapine	D2 Receptor Antagonist	Reduces irritability and psychosis; may also help with chorea but can cause weight gain and metabolic issues	US, Canada, Europe
	Risperidone	D2 and 5-HT2A Receptor Antagonist	Reduces irritability, aggression, and psychosis; can worsen motor symptoms, e.g., bradykinesia and rigidity	US, Canada, Europe
	Aripiprazole	Partial Agonist at D2 and 5-HT1A Receptors	Reduces irritability and psychosis with a lower risk of worsening motor symptoms	US, Canada, Europe
	Clozapine	D2, 5-HT2A Receptor Antagonist	Reduces psychosis and may improve mood, with less risk of motor side effects but requires monitoring for agranulocytosis	US, Canada, Europe
	Quetiapine	D2 and 5-HT2A Receptor Antagonist	Reduces irritability, aggression, and psychosis; generally well-tolerated with less risk of worsening motor symptoms but can cause sedation	US, Canada, Europe
Neuroleptics (Typical)	Haloperidol	D2 Receptor Antagonist	Reduces chorea and psychosis but may significantly worsen motor symptoms and induce parkinsonism	US, Canada, Europe
	Tiapride	D2 Receptor Antagonist	Reduces chorea and psychosis with a lower risk of sedation compared to Haloperidol	Europe
	Fluphenazine	D2 Receptor Antagonist	Reduces chorea and psychosis, similar to Haloperidol, but with a longer duration of action	US, Canada, Europe

Table 2. Antipsychotics with different affinities and potencies for D2 receptors.

Drug Name	D2R Ki (nM)	Affinity and Potency	Potential D2 antagonists side effects (dose-dependent)
Risperidone	~3.0 nM Antagonist	High D2 Blockers	Extrapyramidal side effects (EPSEs) including akathisia, dystonia, and parkinsonism, as well as somnolence, sedation, and impaired cognition
Olanzapine	11-31 nM Antagonist		
Tiapride	320nM Antagonist	Low D2 Blockers	
Aripiprazole	~2.2 nM Partial agonist		
Quetiapine	~245 nM Antagonist		

Table 3. Antidopaminergic medications and their metabolism by CYP2D6.

Table 3. Antidopaminergic medication and metabolism by CYP2D6

Drug	Metabolized by CYP2D6	Metabolites are Active?	Exposure Change Following CYP2D6 Inhibition?	Comments Based on Regulatory Labels (27–29,53,95–97)
Olanzapine	Minor pathway	Unknown	No	CYP2D6 inhibitors do not significantly affect olanzapine levels.
Risperidone	Yes	Yes	Yes	CYP2D6 inhibition has little effect on efficacy because risperidone's metabolite (9-hydroxyrisperidone, a.k.a. paliperidone) is also active as a second-generation neuroleptic.
Tiapride	No data	Unknown	Unlikely	Limited metabolism and no data on CYP2D6 inhibition.
Aripiprazole	Yes	Unknown	Yes	Strong CYP2D6 inhibitors (e.g., quinidine, fluoxetine, paroxetine) will increase exposure to aripiprazole; dose reductions may be needed.
Quetiapine	Minor pathway	No	No	CYP2D6 inhibitors do not appear to significantly affect quetiapine levels.
Fluphenazine	Yes	Unknown	Yes	No data available; caution advised due to potential increased levels.
Haloperidol	Yes	Unknown	Yes	CYP2D6 inhibitors can increase haloperidol levels, especially in poor metabolizers (i.e., a potential 1.7-fold increase in these individuals).
Deutetrabenazine	Yes	Yes	Yes	CYP2D6 inhibitors significantly increase active metabolites; dose adjustment may be needed, especially for individuals deemed poor metabolizers who may experience a 3-4 fold increase in active metabolites. FDA labels caution that "…clinically relevant QT prolongation may occur in some patients treated with AUSTEDO who are CYP2D6 poor metabolizers or are co-administered a strong CYP2D6 inhibitor." (package insert, section 5.7 (54)).

Tetrabenazine	Yes	Yes	Yes	CYP2D6 inhibitors greatly increase active metabolites (i.e., between 3-9 fold increase); dose reduction may be necessary. FDA label cautions "…strong CYP2D6 inhibitors (e.g., paroxetine, fluoxetine, quinidine) markedly increase exposure to [active] metabolites. A reduction in XENAZINE dose may be necessary." (package insert, section 7.1 (28)).

Table 4. Summary of key interventional and observational studies suggesting that the use of ADMs contributes to worsening measures of outcomes in HD, particularly across functional and cognitive domains.

Study Title	Results
Tetrabenazine as anti-chorea therapy in Huntington disease: an open-label continuation study (49)	**Tetrabenazine associated with significant worsening in functional and cognitive measures (Huntington Study Group):** • Functional checklist change vs placebo: -1.2, p=0.02 • SWR change vs placebo: -6.6, p=0.01
Antidopaminergic medication is associated with more rapidly progressive Huntington's disease (4)	**ADMs show significantly worse annual functional decline (REGISTRY dataset):** • TFC change vs placebo: -0.4, p<0.01 • Functional Assessment change vs placebo: -0.9, p<0.001 • Independence Scale (IS) change vs placebo: -2.0, p<0.001
Antidopaminergic treatment is associated with reduced chorea and irritability but impaired cognition in Huntington's disease (Enroll-HD) (3)	**ADMs show significantly greater rate of decline in functional capacity and cognition (Enroll-HD dataset):** • Composite cognitive score change vs placebo: -1.6, p<0.001 • TFC change vs placebo: -0.5, p<0.001 • Independence Scale (IS) change vs placebo: -1.3, p=0.004

Figure 1. Annual change in clinical outcome measures in patients with or without antidopaminergic medications (ADMs).