Understanding Pharmacy Costs and the Changing Treatment Landscape in Huntington's Disease (HD) in the US: A Systematic Literature Review (SLR) and Database Review for Disease-Modifying Therapies (DMT) in Development

EE71

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Introduction and Objective

- HD is a rare autosomal dominant, neurodegenerative disorder caused by a CAG expansion in the *HTT* gene, resulting in the expression of mutant huntingtin protein (mHTT)[1].
- The disease is characterized by cognitive and motor decline, and behavioural symptoms that lead to loss of independence and severe disability[2]. HD is terminal, with onset usually between 30-50 years of age and death occurring ~15 years after diagnosis[2].
- There is no cure or DMT for HD, with current management aiming to address disease symptoms, maximize function, and optimize quality of life[3,4].
- In anticipation of the potential launch of a DMT[4], it is important to understand the current cost of this multidisciplinary treatment approach.
- Therefore, this study aimed to investigate the current pharmacy costs and specific drug costs used in the treatment of HD in the US alongside a review of registered clinical trials to identify potential upcoming DMT in the US.

Methods

- A broad SLR was conducted in Embase in March 2023 to evaluate the economic burden associated with HD.
- Eligible articles were full-text papers published 2008-2023 and conference proceedings published 2020-2023 presenting data relating to healthcare resource utilization or disease-related direct or indirect costs.
- This sub-analysis focused on studies conducted in the US presenting data on treatment costs.
- Studies were screened by two reviewers and reconciled by a third. Data was extracted by a single reviewer, with data number-checked by a second reviewer.

Embase hits: 238 → **Included economic studies: 62** → **Treatment cost studies in the US: 9**

- A clinicaltrials.gov search was conducted in December 2023 using the search term HD to identify potential future treatments.
- Clinical trials of interest had a start date of 2018 onwards, were registered as Phase 2 or Phase 3, with a status of completed, active not recruiting, or recruiting, and were investigating a DMT in the US.

clinicaltrials.gov hits: 23 → **Included clinical trials in the US: 10**

Results

The SLR yielded 9 studies on the cost of HD treatment in the US.

Pharmacy Costs

- Pharmacy costs account for 25%-46% of the total direct healthcare costs[2,3,5,17].
- The average annual pharmacy cost per patient per year ranged from $6,930-$19,182[2,3,5,17], with HD-related pharmacy costs ranging from $5,424-$6,072[3,17](Figure 1).
- As the severity of HD increases the total annual pharmacy costs increase, with pharmacy costs of $860-$14,831 in early-stage disease, $1,989-$15,898 in middle-stage disease, and $3,094-$22,672 in late-stage disease[2,3,6,17].

Figure 1: Annual mean total healthcare costs and pharmacy costs per patient in HD (USD)

Note: Total costs include outpatient, inpatient, and pharmacy costs. HD-related pharmacy costs include HD-related drugs. Exuzides 2020b reported median costs which was not included in this analysis. Costs do differ depending on insurance types. To 2022 reported costs adjusted to 2018[17], Exuzides 2021 reported costs adjusted to 2017[2], Exuzides 2022 reported costs adjusted to 2018[3], and Billet 2022 did not report adjusted cost year[5].

Specific drug costs

- The treatment of motor symptoms of HD incurred the highest costs (Table 1).

Table 1: Annual drug costs for the treatment of different HD symptoms per patient (USD)

Drug	Annual Drug Cost ($)
Motor symptoms	
Valbenazine (median)	76,908[8]
Deutetrabenazine (median)	69,972[8]
Tetrabenazine	24,996[8] (median) - over 70,000[7] (mean)
Psychiatric symptoms	
Risperidone (mean)	7,848[7]
Olanzapine (mean)	6,552[7]
Cognitive impairment	
Rivastigmine (mean)	3,056[7]

Note: Killoran 2012 did not report adjusted cost year[7] and Reynolds 2023 reported costs adjusted to 2019[8]

The **clinicaltrials.gov database search** identified 10 active or completed Phase 2 or 3 trials:

- 5 trials investigated 2 antisense oligonucleotides (Tominersen [ISIS 443139, RO7234292], WVE-003), 2 trials investigated 2 RNA targeting small molecules (PTC518, Branaplam), 2 trials investigated 2 monoclonal antibodies (ANX005, VX15/2503), and 1 trial investigated a gene therapy (intra-striatal rAAV5-miHTT) (Table 2).

Negative News:

- Novartis halted development of Branaplam due to the risk-benefit profile[12].

Positive News:

- Pepinemab (VX15/2503) was granted orphan drug and fast track designation in HD and was well tolerated in patients with early-manifesting HD[19].
- ANX005 was granted fast track designation in 2019 for Guillain-Barré syndrome and has demonstrated clinical improvement in HD[5].
- The ISIS 443139 Phase 1/2 trial for Tominersen was successfully completed in 2017 and, although the follow-on RO7234292 Phase 3 trials were initially halted due to dosing issues[10], when relaunched in younger, less severe patients the results have demonstrated efficacy[11].
- PTC518 has so far been well tolerated with no treatment-related serious adverse events[13].
- A multi-dose trial has been initiated for WVE-003, with early 2024 results being positive and showing a 35% reduction in mHTT[15].
- Although rAAV-miHTT safely and effectively reduced huntingtin in minipigs[16], no results from the human trial have been released to date.

Table 2: Registered clinical trials investigating DMT in HD (US, study start 2018-2023)

Status	Intervention	Phase	Sponsor	Completion Date	Study Location	NCT Number
Completed	ISIS 443139	1/2	Ionis	Nov 2017	Global	NCT02519036
	VX15/2503	2	Vaccinex	Aug 2020	US	NCT02481674
	ANX005	2	Annexon	Jan 2022	US only	NCT04514367
	RO7234292	3	Hoffmann-La Roche	Mar 2022	Global	NCT03761849
	RO7234292	3	Hoffmann-La Roche	Mar 2022	Global	NCT03842969
	Branaplam	2	Novartis	Oct 2023	Global	NCT05111249
Recruiting	PTC518	2	PTC	Jul 2024	Global	NCT05358717
	WVE-003	1/2	Wave	Dec 2024	Global	NCT05032196
	Tominersen	2	Hoffmann-La Roche	Apr 2027	Global	NCT05686551
	rAAV5-miHTT	1/2	UniQure	Jun 2029	US only	NCT04120493

Conclusion

- The Pharmacy costs associated with interventions aiming to control the symptoms of HD are substantial, with these costs increasing as HD progresses and symptom severity increases. The treatment of motor symptoms incurs the highest drug costs, with the treatment of psychiatric symptoms and cognitive impairment incurring a much lower annual drug cost.
- Although the current treatment options only alleviate symptoms, there are several interventions currently in development providing hope for a future DMT. Many of these interventions show early promise; however, there have been mixed results for some – with safety concerns for Branaplam, and Tominersen's pivotal trial needing to be relaunched in an earlier-stage patient population. Clearly the development of a successful DMT in HD is difficult and, despite the early promise of these positive results, approval of a DMT may take some time yet.
- The significant economic burden associated with the symptomatic treatment of HD illustrates the importance of developing a DMT that can prevent or slow disease progression for patients with HD, particularly at earlier stages of disease where symptom management is less costly.

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