MED-MSL-HD-US-0006

Enroll-HD: Chorea Characteristics and Treatment Patterns in Patients with Huntington Disease

NEUROCRINE® BIOSCIENCES

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Enroll-HD Background

Enroll-HD

- Enroll-HD is the largest, worldwide, prospective, observational study for individuals who have (or are at-risk for) Huntington disease (HD), with the goal of clinically following patients over time in a real-world setting[1]

- This observational registry study is supported by the CHDI Foundation (NCT01574053) and contains:[1,2]

>21,000 Participants

155 Clinical Sites

22 Nations Across 4 Continents

1. What is Enroll-HD? https://www.enroll-hd.org/for-hd-families/about-this-study/. Accessed July 11, 2022. 2. Clinicaltrials.gov. https://clinicaltrials.gov/ct2/show/NCT01574053 Accessed July 11, 2022.

Enroll-HD Study Rationale

Objective:

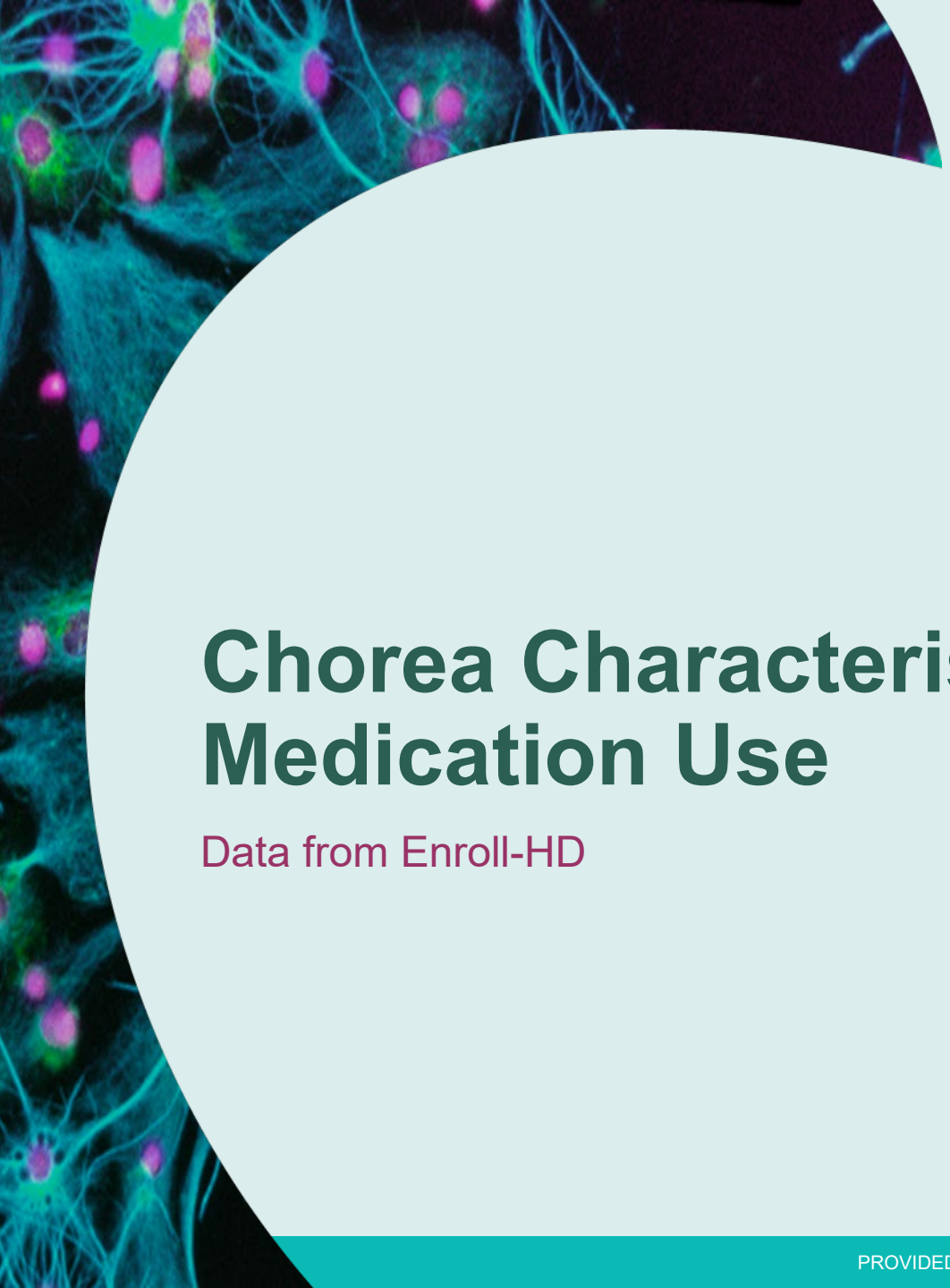
To better understand the patient characteristics, medication use and treatment patterns of chorea in HD

Enroll-HD Phase 1:

Chorea Characteristics and Medication Use

Enroll-HD Phase 2:

Longitudinal Treatment Patterns



Chorea Characteristics and Medication Use

Data from Enroll-HD

Objective & Study Design

Objective

To assess disease characteristics of individuals with manifest HD at the most recent Enroll-HD registry visit and evaluate treatments for chorea taken throughout the registry period

Study Design

- Analyses were based on the Periodic Dataset 4.0 of the Enroll-HD registry
  - Patient data from June 2012 to October 2018
- Enroll-HD participants met the following criteria for inclusion at their most recent visit:

≥ 18 years

Manifest HD
Defined as diagnostic confidence level (DCL) of 4 (“motor abnormalities that are unequivocal signs of HD”) on the UHDRS® at most recent visit

North American clinical site

HD, Huntington disease; TFC, Total Functional Capacity; UHDRS, Unified Huntington’s Disease Rating Scale

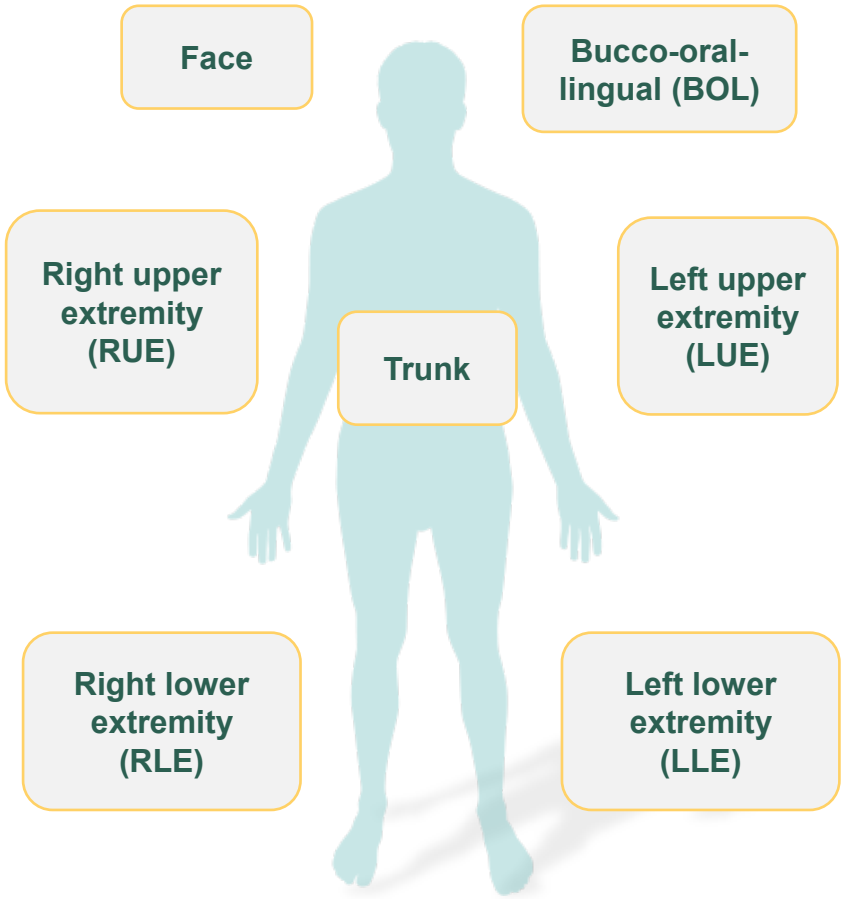
Furr-Stimming EE, et al. AAN 2021; Presented virtually.

Study Design Cont.

- Participants were categorized by disease progression, defined by UHDRS® TFC score as follows:

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

- The following patient and disease characteristics were assessed at the most recent visit
  - Sociodemographic characteristics,
  - UHDRS® TMS and TMC scores for 7 body regions
- Chorea medications taken at any time during the registry period were also assessed
- Data were analyzed descriptively



HD, Huntington disease; TFC, Total Functional Capacity; TMC, Total Motor Scale; UHDRS, Unified Huntington's Disease Rating Scale

Furr-Stimming EE, et al. AAN 2021; Presented virtually.

Patient Characteristics

Total of 2205 participants were categorized as manifest HD (DCL of 4 at most recent visit)

53.9 years

Mean age of participants with manifest HD

The majority of participants were:

- **TFC stages I – III (90.8%)**
- **Female (52.4%)**
- **White (89.0%)**

Mean UHDRS® TMS score* was 39.6

- **Score range from 24.5 (stage I) to 77.4 (stage V)**

Mean UHDRS® TMC score was 9.3

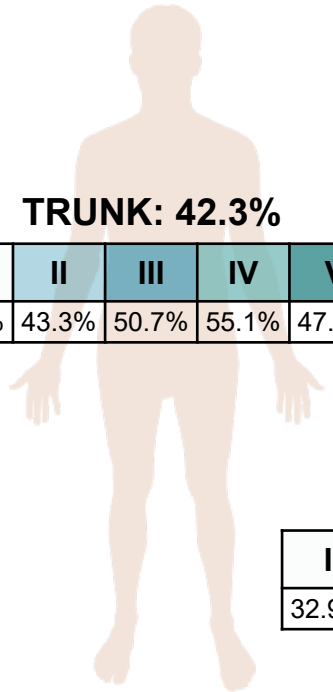
- **Score range from 7.9 (stage I) to 10.7 (stage IV)**

*Based on available data: n=2190 for all stages; n=565 for stage I; n=878 for stage II; n=546 for stage III; n=155 for stage IV; n=42 for stage V.
DCL, diagnostic confidence level; HD, Huntington disease; TFC, Total Functional Capacity; TMC, Total Motor Scale; UHDRS, Unified Huntington's Disease Rating Scale
Furr-Stimming EE, et al. AAN 2021; Presented virtually.

Chorea Characteristics

	Manifest (All Stages) (N=2205)	Manifest Subgroups[b]				
		Stage I (n=569)	Stage II (n=884)	Stage III (n=550)	Stage IV (n=156)	Stage V (n=42)
Participants with chorea score ≥2 in any body region[a], n (%)	1552 (70.4)	348 (61.2)	648 (73.3)	405 (73.6)	121 (77.6)	29 (69.0)

Percent Participants by Stage with ≥2 Chorea Score By Body Region



BOL: 33.8%

I	II	III	IV	V
18.5%	34.0%	42.7%	53.2%	50.0%

FACE: 32.8%

I	II	III	IV	V
20.2%	32.9%	39.1%	51.3%	52.4%

TRUNK: 42.3%

I	II	III	IV	V
29.0%	43.3%	50.7%	55.1%	47.6%

RUE: 49.1%

I	II	III	IV	V
39.0%	52.7%	54.0%	50.0%	45.2%

LUE: 48.8%

I	II	III	IV	V
38.0%	53.4%	52.7%	51.3%	42.9%

RLE: 40.7%

I	II	III	IV	V
33.6%	42.8%	44.2%	42.9%	42.9%

LLE: 40.9%

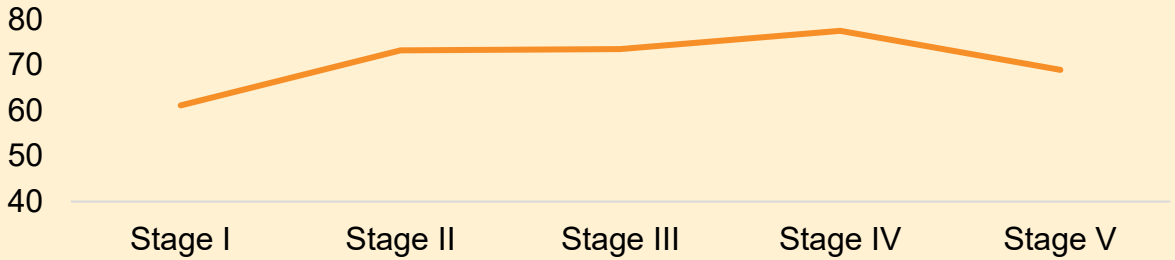
I	II	III	IV	V
32.9%	43.7%	44.4%	43.6%	40.5%

[a]Maximal chorea score ≥2 defined as "mild common or moderate intermittent" to "marked prolonged." [b]Four participants had missing TFC data.
BOL, bucco-oral-lingual; LLE, left lower extremity; LUE, left upper extremity; RLE, right lower extremity; RUE, right upper extremity; TFC, Total Functional Capacity.
Furr-Stimming EE, et al. AAN 2021; Presented virtually.

Chorea Characteristics Cont.

		Manifest Subgroups[b]				
	Manifest (All Stages) (N=2205)	Stage I (n=569)	Stage II (n=884)	Stage III (n=550)	Stage IV (n=156)	Stage V (n=42)
Participants with chorea score ≥2 in any body region[a], n (%)	1552 (70.4)	348 (61.2)	648 (73.3)	405 (73.6)	121 (77.6)	29 (69.0)

Percentage of participants with chorea score ≥2 in any body region



- The proportion of patients with a maximal chorea score ≥2 increased from stage I (61.2%) to stage IV (77.6%) and then appeared to plateau or decrease by stage V
- This interpretation is challenged by the relatively small number of participants in manifest TFC stage V in this study (n=42)

[a]Maximal chorea score ≥2 defined as "mild common or moderate intermittent" to "marked prolonged." [b]Four participants had missing TFC data.
BOL, bucco-oral-lingual; LLE, left lower extremity; LUE, left upper extremity; RLE, right lower extremity; RUE, right upper extremity; TFC, Total Functional Capacity.
Furr-Stimming EE, et al. AAN 2021; Presented virtually.

Medications Used to Treat Chorea

	Manifest (All Stages) (N=2205)	Manifest Subgroups[a]				
		Stage I (n=569)	Stage II (n=884)	Stage III (n=550)	Stage IV (n=156)	Stage V (n=42)
Medication, n (%)	**647 (29.3)**	76 (13.4)	237 (26.8)	236 (42.9)	70 (44.9)	26 (61.9)
Tetrabenazine monotherapy	233 (36.0)	32 (42.1)	79 (33.3)	91 (38.6)	22 (31.4)	9 (34.6)
Tetrabenazine + antipsychotic[b] or other medication[c]	68 (10.5)	1 (1.3)	26 (11.0)	21 (8.9)	13 (18.6)	7 (26.9)
Antipsychotic monotherapy[b]	224 (34.6)	25 (32.9)	94 (39.7)	78 (33.1)	20 (28.6)	6 (23.1)
Antipsychotic[b] + other medication[c]	25 (3.9)	2 (2.6)	6 (2.5)	10 (4.2)	6 (8.6)	1 (3.8)
Other medication[c]	97 (15.0)	16 (21.1)	32 (13.5)	36 (15.3)	9 (12.9)	3 (11.5)

[a]Four participants had missing TFC data.
[b]Antipsychotics included: aripiprazole, asenapine maleate, brexpiprazole, cariprazine, chlorpromazine, clozapine, fluphenazine, haloperidol or haloperidol decanoate, iloperidone, lurasidone or lurasidone hydrochloride, olanzapine, quetiapine or quetiapine fumarate, paliperidone or paliperidone palmitate, perphenazine, pimavanserin, pimozide, prochlorperazine, risperidone, ziprasidone or ziprasidone hydrochloride.
[c]Other medications included: amantadine or amantadine hydrochloride; baclofen; carbidopa; carbidopa, levodopa; clonazepam; gabapentin; dextromethorphan hydrobromide, quinidine sulfate; donepezil hydrochloride; lamotrigine; levetiracetam; levodopa; mirtazapine; paroxetine hydrochloride; ropinirole or ropinirole hydrochloride; trihexyphenidyl; ubidecarenone; valproate semisodium or valproate sodium or valproic acid; cannabis sativa; investigational drug.
Deutetrabenazine was not coded in periodic dataset 4.0.

- Among participants with manifest HD, 29.3% were taking a medication to treat chorea
- Of 319 patients taking tetrabenazine, 301 (94.4%) were taking it for chorea *(deutetrabenazine was not coded in the registry dataset as it was not widely available before the 2018 cutoff date)*

HD, Huntington disease

Furr-Stimming EE, et al. AAN 2021; Presented virtually.

Summary

- In this retrospective analysis of real-world data from the Enroll-HD registry, chorea severity increased with more advanced stages of disease and occurred across all body regions
- 70.4% of participants in this study with manifest HD had “mild common/moderate intermittent” to “marked prolonged” chorea
- 29.3% were prescribed a medication to treat chorea
- Study limitation: inherent constraints of a real-world database with data available only up to 2018, and a small sample size in manifest TFC stage V

HD, Huntington disease; TFC, Total Functional Capacity.

Furr-Stimming EE, et al. AAN 2021; Presented virtually.

Longitudinal Treatment Patterns for Chorea in HD

Data from Enroll-HD

Objective

To better understand treatment patterns for chorea using longitudinal data from the Enroll-HD registry

- Treatments for chorea include:[1,2]
  - FDA-approved medications (e.g., VMAT2 inhibitors)
  - Off-label medications (e.g., antipsychotics, benzodiazepines)
- In the previous analysis of Enroll-HD, chorea severity increased as HD progressed[3]
  - However, <30% of patients with HD received a medication for chorea regardless of their disease stage

FDA, United States Food and Drug Administration; HD, Huntington disease; VMAT2, vesicular monoamine transporter 2

1. Armstrong MJ, Miyasaki JM. *Neurology*. 2012;79(6):597-603 2. Ferreira JJ et al. *Mov Disord*. 2022;37(1): 25-35. 3. Furr Stimming EE et al. AAN 2021; Presented virtually.

Study Design

- Analyses based on the Periodic Dataset 5.0 of the Enroll-HD registry
  - Patient data from June 2012 to October 2020
- Enroll-HD patients who met the following criteria at their most recent visit were included for analysis:

≥ 18 years and from a **North American** clinical site

CAG repeat length ≥36

Manifest HD
Defined as diagnostic confidence level (DCL) of 4 (“motor abnormalities that are unequivocal signs of HD”) on the UHDRS® **at baseline and all available visits**

- Presence of chorea was defined as UHDRS® Total Maximal Chorea (TMC) score ≥2 (“mild common or moderate intermittent” to “marked prolonged”) in any body region

HD, Huntington disease; UHDRS, Unified Huntington’s Disease Rating Scale.

Furr Stimming, EE et al, AAN 2022; Seattle, WA.

Study Design Cont.

Medications prescribed for chorea (as indicated in the Enroll-HD database) were categorized as follows:

VMAT2 Inhibitors alone:	Antipsychotics (APs) alone*	Other medications	Combination:
tetrabenazine, deutetrabenazine		**(i.e., not VMAT2 inhibitor or AP)**	**≥2 different medications from previous 3 categories (e.g., VMAT2 inhibitor + AP)**

*This analysis did not include antipsychotics prescribed primarily for a psychiatric disorder (or other non-chorea condition). Clinicians/investigators were required to choose only 1 indication for each medication. Therefore, it is unknown whether any medication (e.g., antipsychotic) was being used to treat multiple conditions.

AP, antipsychotic; VMAT2, vesicular monoamine transporter 2

Furr Stimming, EE et al, AAN 2022; Seattle, WA.

Patient Characteristics

	Without Clinical Chorea (n=83)	With Clinical Chorea (n=2507)
Total number of visits	242	6678
Average number of visits	2.9	2.7
Follow-up duration, mean (SD), months[a]	32.1 (24.6)	22.8 (22.9)
Age at enrollment, mean (SD), years	44.9 (17.4)	53.0 (12.6)
Age at diagnosis, mean (SD), years	40.4 (17.0)	49.0 (12.6)
Female, n (%)	49 (59.0)	1302 (51.9)
Race or ethnicity, n (%)		
White/Caucasian	73 (88.0)	2236 (89.2)
Black/African American	4 (4.8)	83 (3.3)
Hispanic/Latino origin	3 (3.6)	73 (2.9)
Other[b]	3 (3.6)	115 (4.6)
UHDRS scores, mean (SD)[c]		
Total Maximal Chorea (TMC)	0.3 (0.5)	10.0 (4.7)
Total Motor Score (TMS)	42.7 (23.0)	39.4 (18.2)
Total Functional Capacity (TFC)	5.6 (3.5)	7.9 (3.3)

96.8%
of patients presented with chorea

[a]Patients who switched between "with clinical chorea" and "without clinical chorea" during the study were counted in both categories (n=2542 and n=177, respectively).

[b]Includes American Indian/Native American/Amerindian, Asian, mixed (non-specified), and other (non-specified).

[c]Based on the number of visits with available data, as follows: TMC (n=6678 [with chorea], n=242 [without chorea]); TMS (n=6643, n=236); TFC (n=6662, n=241).

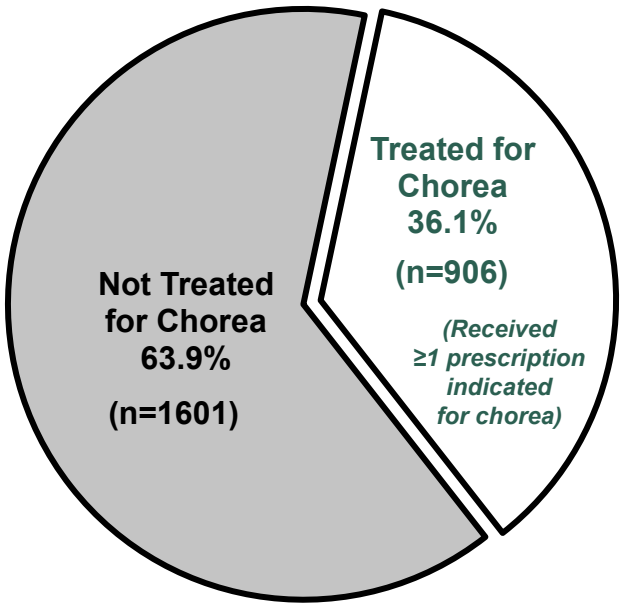
SD, standard deviation; UHDRS, Unified Huntington's Disease Rating Scale.

Furr Stimming, EE et al, AAN 2022; Seattle, WA.

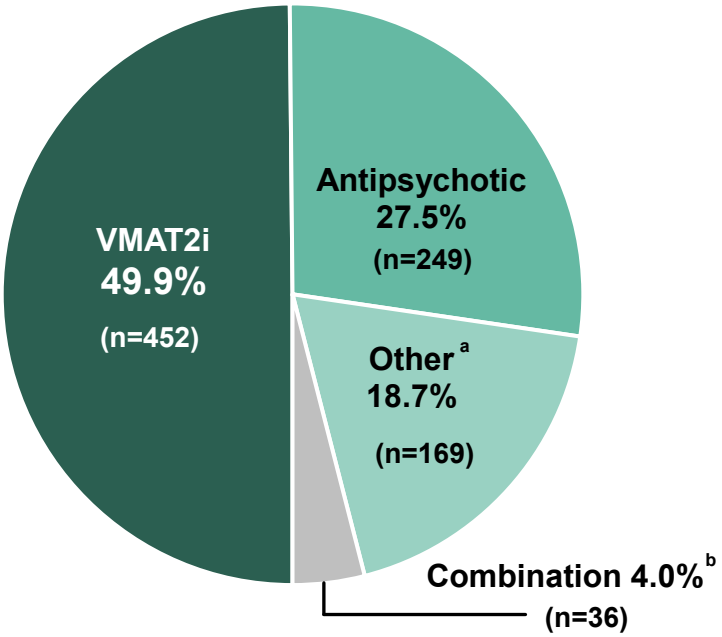
Proportion of Treated/Untreated Patients with Chorea and First-Line Medications in Treated Patients

Only 906 (36.1%) of 2507 patients with chorea were prescribed an anti-chorea medication at any visit, with VMAT2 being the most common first-line treatment

Patients with Chorea (N=2507) Defined as UHDRS® TMC Score ≥2

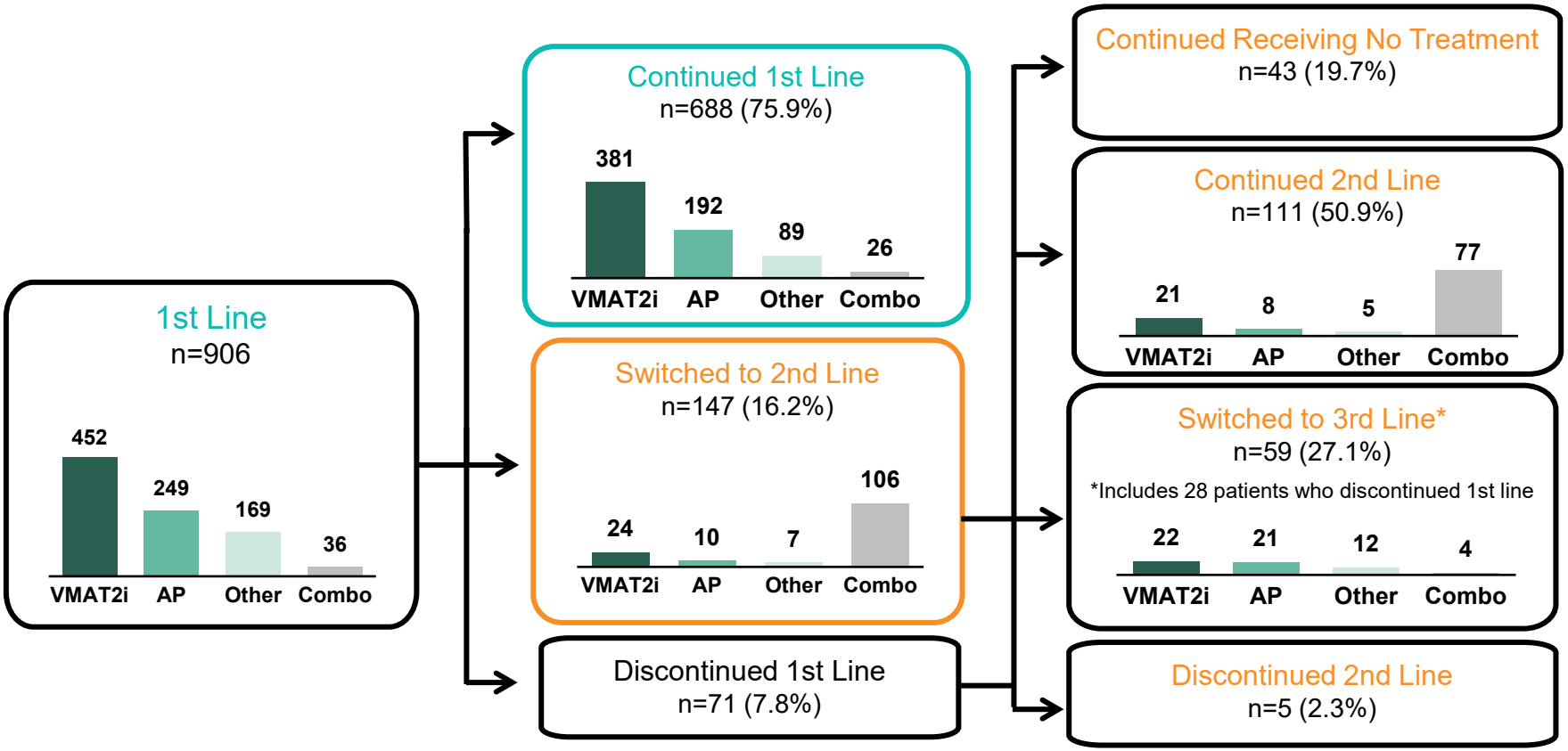


First-Line Medications for Chorea in Treated Patients (N=906)



[a]Any medication except for a vesicular monoamine transporter 2 inhibitor (VMAT2i) or antipsychotic.
[b]Any combination of a VMAT2 inhibitor, antipsychotic, and/or other medication.
UHDRS, Unified Huntington's Disease Rating Scale.
Furr Stimming, EE et al, AAN 2022; Seattle, WA.

Longitudinal Treatment Patterns for Chorea: Flowchart

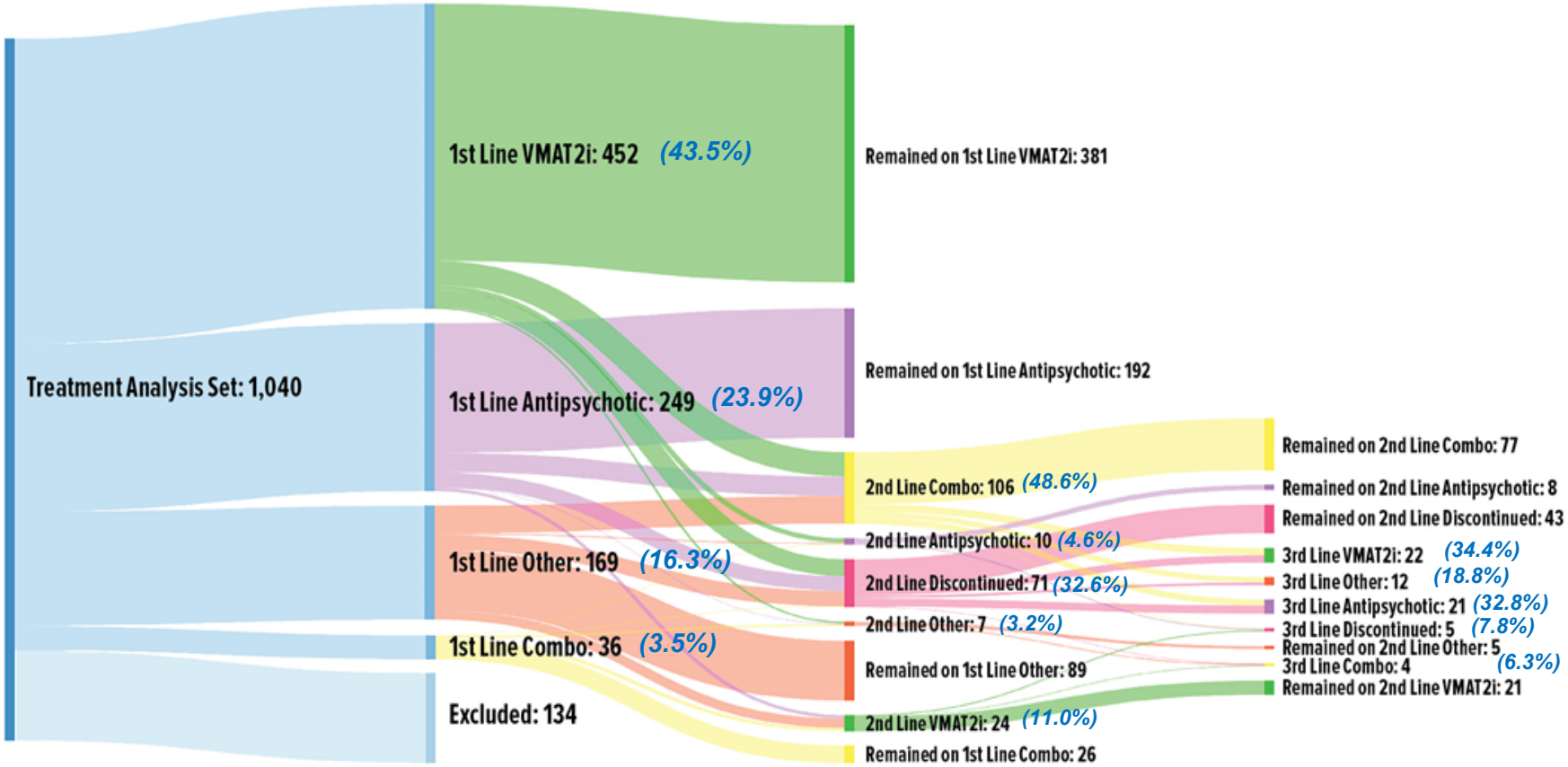


AP, antipsychotic; Combo, any combination of chorea medications; Other, medication other than VMAT2i or AP; VMAT2i, vesicular monoamine transporter 2 inhibitor

Furr Stimming, EE et al, AAN 2022; Seattle, WA.

Longitudinal Treatment Patterns for Chorea: Sankey Diagram

- Most patients continued their treatment with VMAT2 inhibitors or antipsychotics
- Patients who were prescribed other therapies changed treatments more frequently



AP, antipsychotic; Combo, any combination of chorea medications; Other, medication other than VMAT2i or AP; VMAT2i, vesicular monoamine transporter 2 inhibitor.

Furr Stimming, EE et al, AAN 2022; Seattle, WA.

Mean Treatment Duration (Months)

	VMAT2i	Antipsychotic	Other[a]	Combination[b]
First-line, n	452	249	169	36
Mean (SD)	28.8 (29.2)	41.2 (45.0)	37.0 (36.8)	38.8 (32.8)
Min, max	1, 389	1, 380	1, 234	2, 127
Second line, n	24	10	7	106
Mean (SD)	14.0 (9.1)	12.5 (7.0)	60.8 (107.2)	24.5 (24.2)
Min, max	4, 38	4, 23	4, 302	1, 118

[a]Any medication except a vesicular monoamine transporter 2 inhibitor (VMAT2i) or antipsychotic.
[b]Any combination of a VMAT2i, antipsychotic, and/or other medication.

AP, antipsychotic; Combo, any combination of chorea medications; Other, medication other than VMAT2i or AP; VMAT2i, vesicular monoamine transporter 2 inhibitor
Furr Stimming, EE et al, AAN 2022; Seattle, WA.

Summary

- In this Phase 2 retrospective analysis of real-world data from the Enroll-HD registry, 96.8% of patients with manifest HD presented with chorea at any study visit
  - 36.1% of patients were prescribed a medication that was specifically indicated for chorea *(higher than Phase 1 results)*
- Most patients on an anti-chorea medication tended to stay on their initially prescribed therapy, most commonly a VMAT2 inhibitor or antipsychotic
  - Those who switched to a second- or third-line treatment often received a combination therapy (e.g., VMAT2 inhibitor plus antipsychotic)
- Results are limited by the inherent constraints of a natural history database with data available through October 2020
- Antipsychotics that were not specifically listed as being used to treat chorea were excluded from this analysis. It is possible that some of these medications – although primarily indicated for non-chorea conditions (e.g., psychotic disorder) – were also being used to help manage chorea

HD, Huntington disease; VMAT2, vesicular monoamine transporter 2.

Furr Stimming, EE et al, AAN 2022; Seattle, WA.