Updates in Hyperkinetic Disorders (TD and HD)

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AMDAPP
Association of Movement Disorder Advanced Practice Providers

Christa Cooper – Relevant Financial Relationships

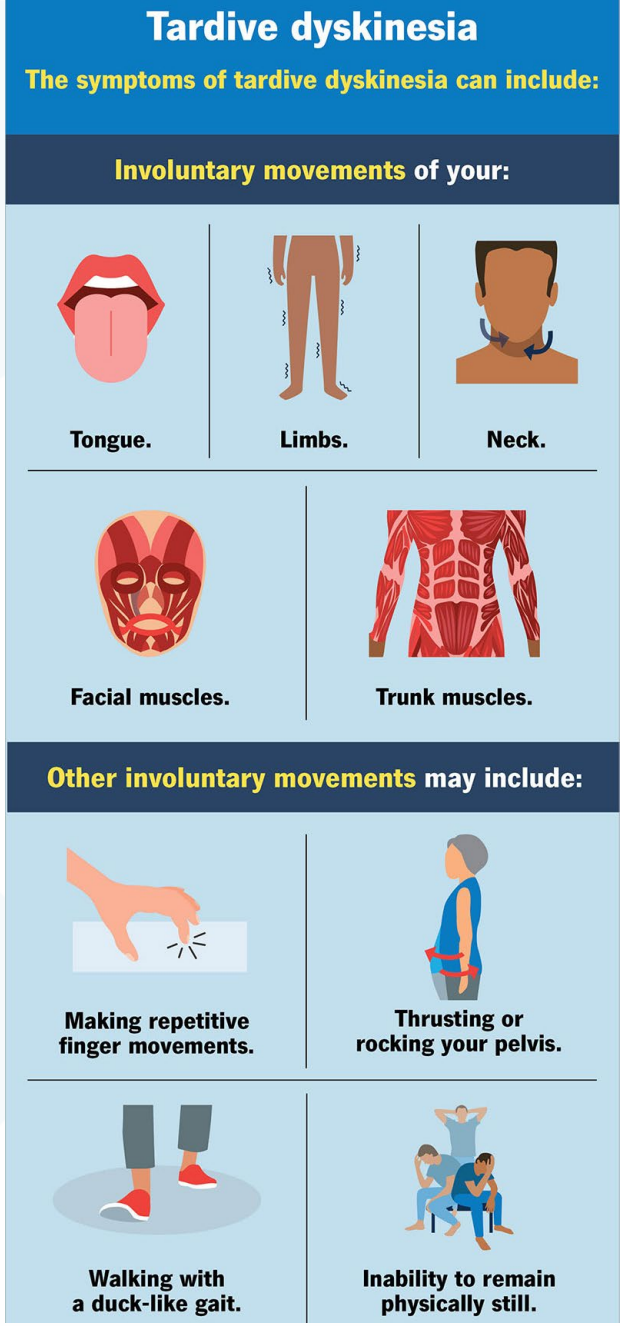
- Site investigator for research/trial supported by Roche.
- Speakers' Bureau, consultant, and/or advisory board member for Teva, Neurocrine, and Abbott.

All relevant financial relationships have been mitigated

Tardive Dyskinesia

- Medication induced hyperkinetic movement disorder associated with the use of dopamine-receptor blocking agents (DRBAs)
  - First and second-generation antipsychotics
  - Some anti-nausea medications

- Symptoms begin after:
  - 3 months of DRBA exposure (1 month if >60 y/o)
  - Within 8 weeks of withdrawal (4 weeks for injectable)



Tardive Dyskinesia Symptoms

Face	Trunk	Extremities
• Chewing • Lip Smacking • Tongue thrusting • Excessive blinking • Cheek bulging	• Rocking • Hip thrusts • Shoulder shrugging • Swaying	• “Piano playing” fingers • Toe tapping • Hyperextended toes

Abnormal Involuntary Movement Scale (AIMS)

- Face
  - 4 subcategories
- Upper extremities
- Lower Extremities
- Trunk

- 0-4 scale
  - 0=none
  - 1=minimal, may be normal
  - 2=mild
  - 3=moderate
  - 4=severe

- Max score = 28

Abnormal Involuntary Movement Scale (AIMS)

Instructions: Complete the examination procedure before making ratings. Circle score for each item.

Patient Name:	Date:	None	Minimal, may be extreme normal	Mild	Moderate	Severe
Facial and Oral Movements						
1. Muscles of Facial Expression e.g., movements of forehead, eyebrows, periorbital area, cheeks; Include frowning, blinking, smiling, grimacing		0	1	2	3	4
2. Lips and Perioral Area e.g., puckering, pouting, smacking		0	1	2	3	4
3. Jaw e.g., biting, clenching, chewing, mouth opening, lateral movement		0	1	2	3	4
4. Tongue Rate only increases in movement both in and out of mouth, NOT inability to sustain movement		0	1	2	3	4
Extremity Movements						
5. Upper (arms, wrists, hands, fingers) Include choreic movements (i.e., rapid, objectively purposeless, irregular, spontaneous); athetoid movements (i.e., slow, irregular, complex, serpentine). DO NOT include tremor (i.e., repetitive, regular, rhythmic).		0	1	2	3	4
6. Lower (legs, knees, ankles, toes) e.g., lateral knee movement, foot tapping, heel dropping, foot squirming, inversion and eversion of foot		0	1	2	3	4
Trunk Movements						
7. Neck, shoulders, hips e.g., rocking, twisting, squirming, pelvic gyrations		0	1	2	3	4
Global Judgments						
8. Severity of abnormal movements		0	1	2	3	4
9. Incapacitation due to abnormal movements		0	1	2	3	4
10. Patient's awareness of abnormal movements (rate only patient's report) 0 = not aware; 1 = aware, no distress; 2 = aware, mild distress; 3 = aware, moderate distress; 4 = aware, severe distress		0	1	2	3	4
Dental Status						
11. Current problems with teeth and/or dentures?		No	Yes			

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First-Tier Medications

- VMAT2 Inhibitors
  - Tetrabenazine
  - Deutetrabenazine
  - Valbenazine

VMAT2 inhibitors

- Tetrabenazine
  - Not specifically FDA approved for TD
  - 50-150mg a day in divided doses

- Deutetrabenazine (Austedo)
  - BID dosing
  - Once daily dosing (Austedo XR) starting at 12mg → 48mg
    - Approved in 2023
  - Titration pack available

- Valbenazine (Ingrezza)
  - Once daily dosing of 40mg, 60mg, or 80mg
  - Comes in a sprinkle formulation for patients with dysphagia or pill aversion
    - Approved in 2024

Neurocrine (NBI-1065890)

- Selective VMAT2 inhibitor
- Phase I started March 2024
  - Safety, tolerability, and pharmacokinetics in healthy adults
  - Results pending
- Potential Phase II starting 2026?

Second-Tier Medications

- Clonazepam
- Amantadine
- Ginkgo biloba extract

Clonazepam

- Double-blind RCT (n=19)
  - Clonazepam vs placebo
  - 4-week crossover design with 2-week wash-out

- Clonazepam 2-3.5mg/day
  - 37% reduction in abnormal movements compared to placebo
  - Side effects: sedation and ataxia
  - Effect waned after 5-8 months

Amantadine

- Double-blind RCT (n=22)
  - 2-week crossover design with 4-day washout

- Amantadine 400mg/day vs placebo
  - Statistically significant reduction in AIMS
  - 22% reduction in AIMS scores
  - No worsening of psychiatric symptoms

Ginkgo Biloba

- 12-week double blinded clinical trial in TD patients (n=157)
  - Concentrated ginkgo biloba extract (EGb761)
  - 80mg TID vs placebo
- AIMS measured at baseline and 12 weeks
  - >50% of participants in treatment group had ≥30% decrease in AIMS score
  - Treatment group had significant reduction in AIMS score compared to placebo

- 2023 Case Study
  - 36 y/o male with history of schizophrenia and TD. AIMS=12 at baseline.
  - Could not tolerate VMAT2 inhibitor
  - 80mg TID of ginkgo biloba
  - After 8 weeks AIMS=4 (~66% reduction)
  - After 24 weeks AIMS=1 (~91% reduction)

Third-Tier Medications

- These options have insufficient evidence but could be considered:
  - Levetiracetam
  - Vitamin B6
  - Melatonin
  - Baclofen
  - Propranolol
  - Vitamin E
  - Zolpidem
  - Zonisamide

Botulinum Toxin

- Several open-label retrospective reports support use in:
  - Oromandibular dystonia
  - Lingual dystonia
  - Cervical dystonia

- Similar response to those with idiopathic dystonia

Deep Brain Stimulation (DBS) for TD

- Trial of bilateral GPi DBS in patients with severe TD (n=19)
- Assessed at baseline, 3, 6, and 12 months
- At 6 months all patients had >40% decrease in Extrapyramidal Symptoms Rating Scale and this was maintained at 1 year
- Despite psychiatric comorbidities, tolerability for DBS was excellent
- Pallidal DBS should be considered in severe, medication refractory TD

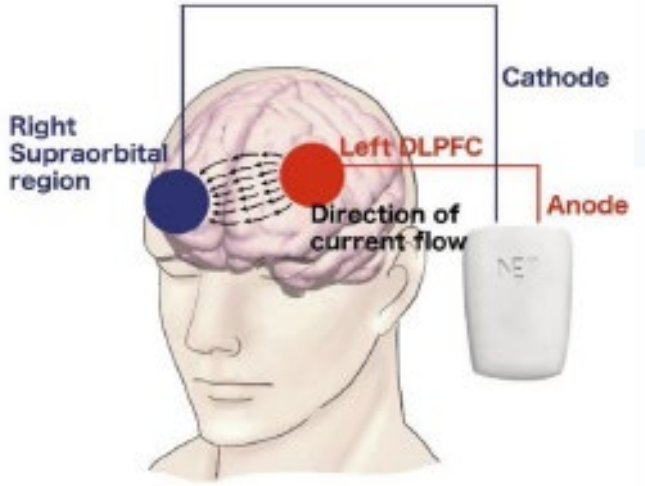
Electroconvulsive Therapy for TD

- 2024 Case report of 25 y/o with severe, medication resistant TD
  - Admitted for ECT
  - Baseline AIMS = 10

- ECT twice weekly x 6 weeks
  - AIMS at discharge = 2

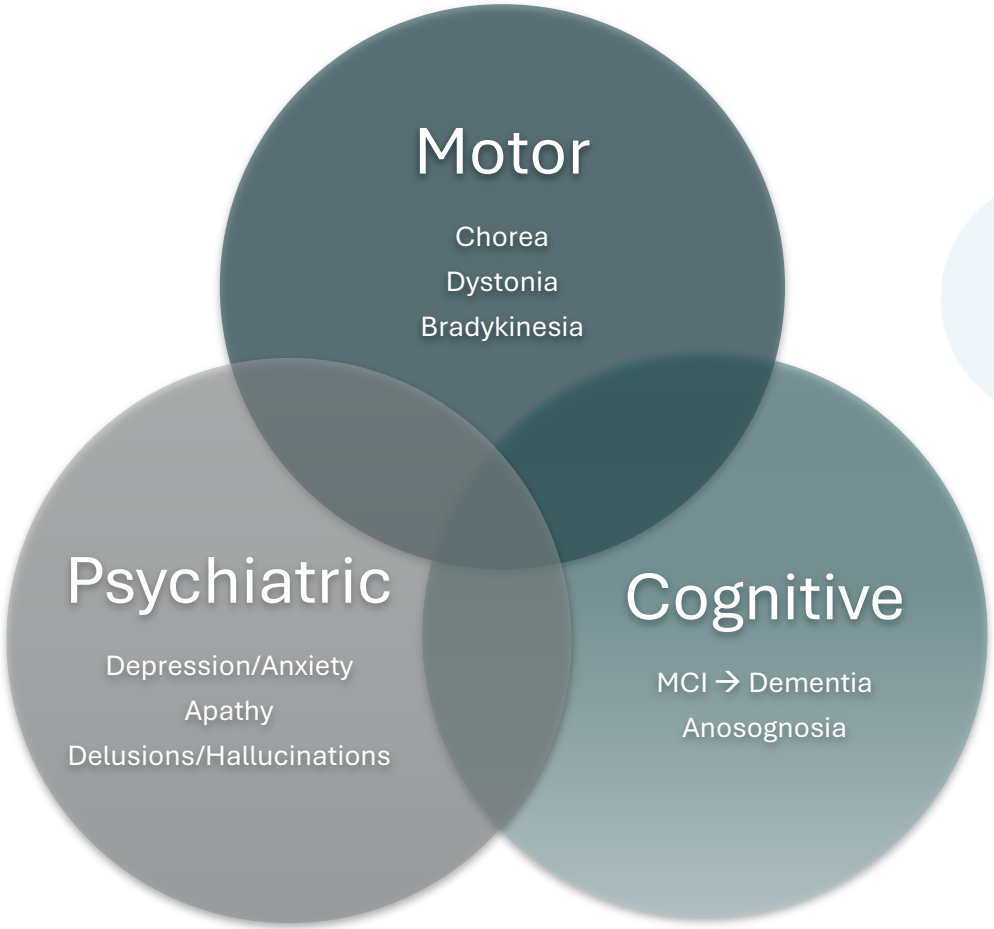
- Literature review of ECT for TD (n=32)
  - 84% had at least partial response to ECT
  - 9% worsened

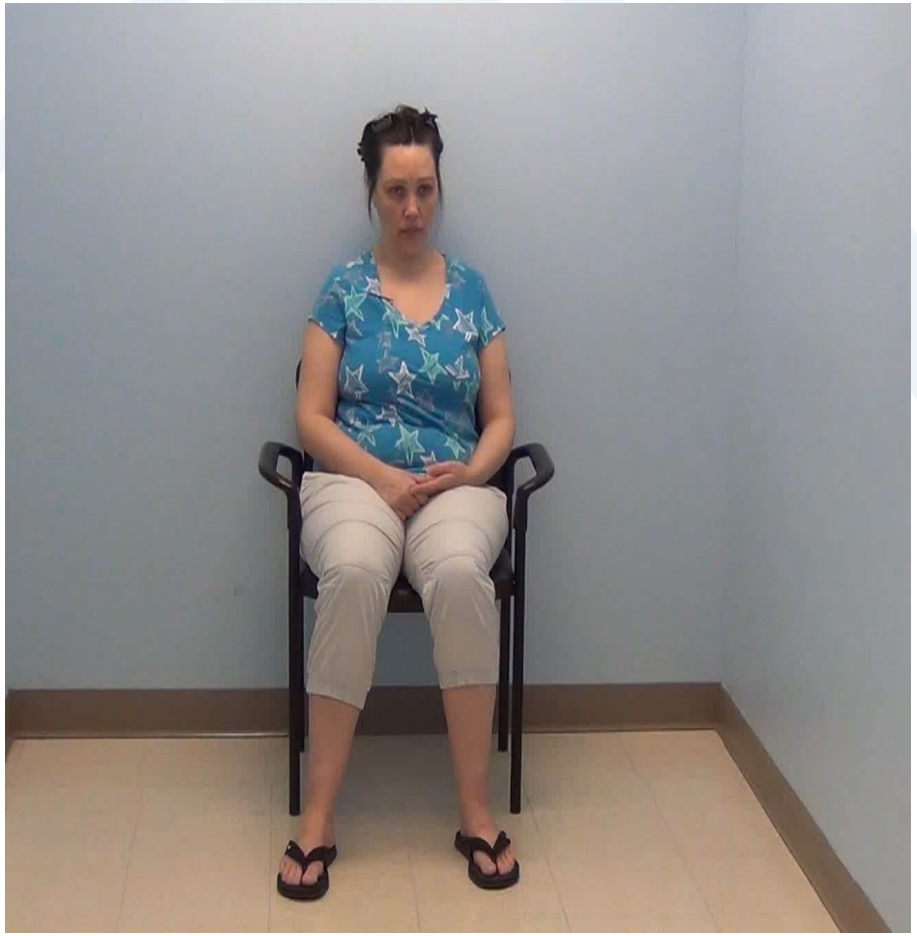
Transcranial direct current stimulation



- 2024 RCT of tDCS for TD (n=64)
  - tDCS: non-invasive brain stimulation using weak electrical current
- Randomized to treatment (n=35) or sham (n=29)
  - Fifteen 30-minute sessions of tDCS with intensity of 2mA
- Primary outcome was AIMS score
  - Statistically significant reduction in AIMS compared to sham
- 50% of participants in treatment group had ≥30% reduction in AIMS
  - Improvement seen in facial-oral symptoms but not extremities or trunk
- Most common side effect was tingling sensation

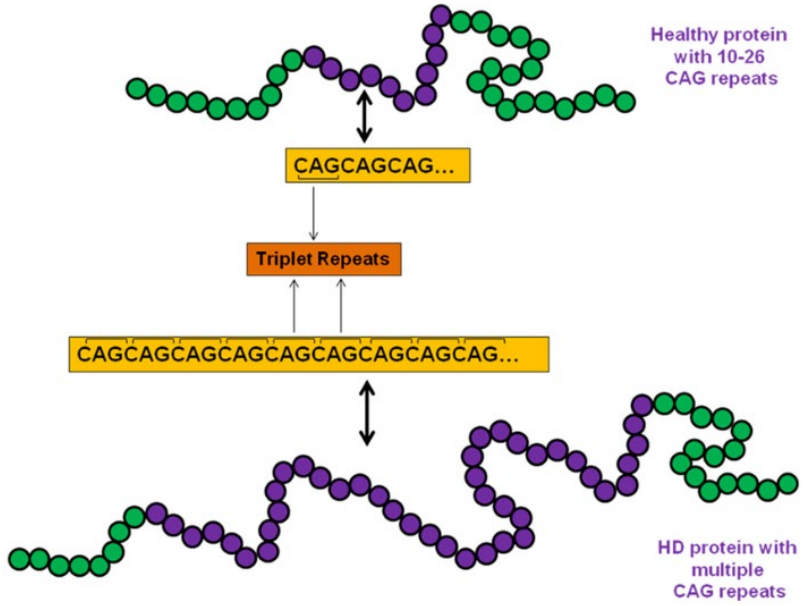
Huntington's Disease

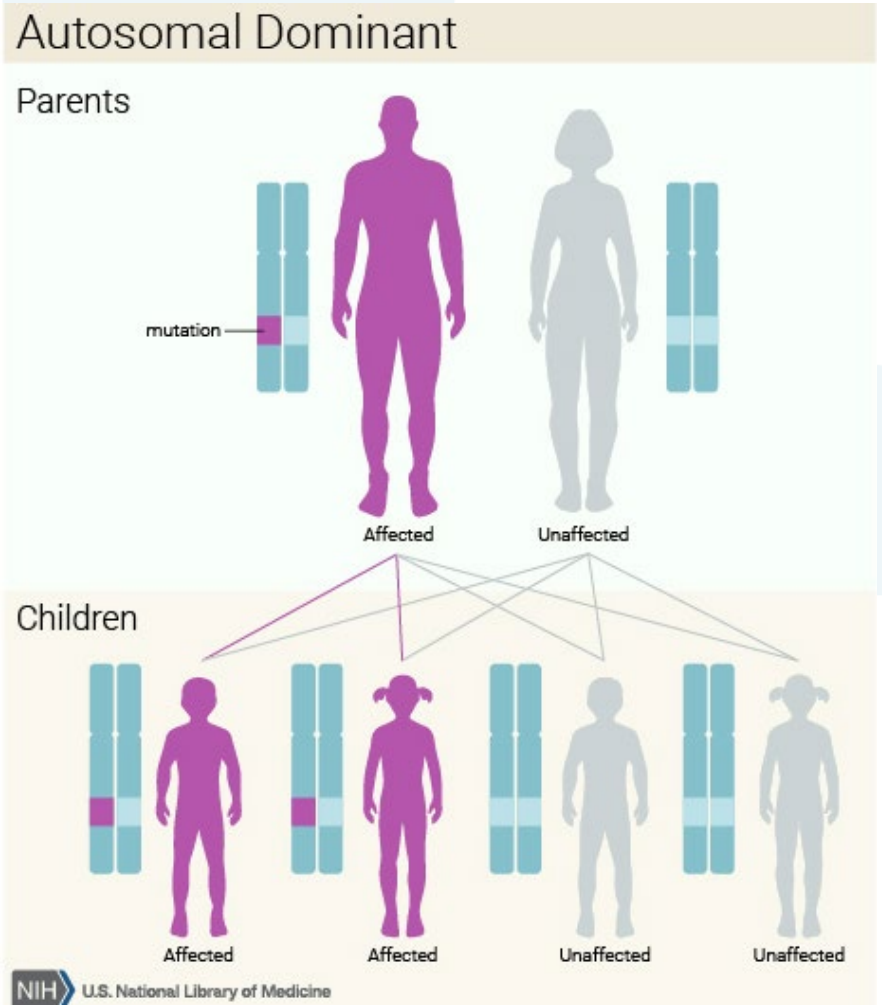




HD Genetics

- Autosomal dominant
  - Offspring at 50% risk of inheriting the disease
- Causative gene discovered in 1993
  - Expanded CAG repeat on chromosome 4





HD Genetics

Repeat length of expanded allele	Phenotype	Interpretation of repeat length
≤26	Normal	No risk of developing HD
27-35	Borderline, intermediate allele	Unstable. Typically, will not develop symptoms in a normal lifespan but offspring are at higher risk.
36-39	Reduced penetrance	Abnormal, unstable. May develop symptoms at an advanced age. Offspring at increased risk due to possible gene expansion.
≥40	Full penetrance	Abnormal, will develop HD during a normal life span. Offspring at 50% risk.

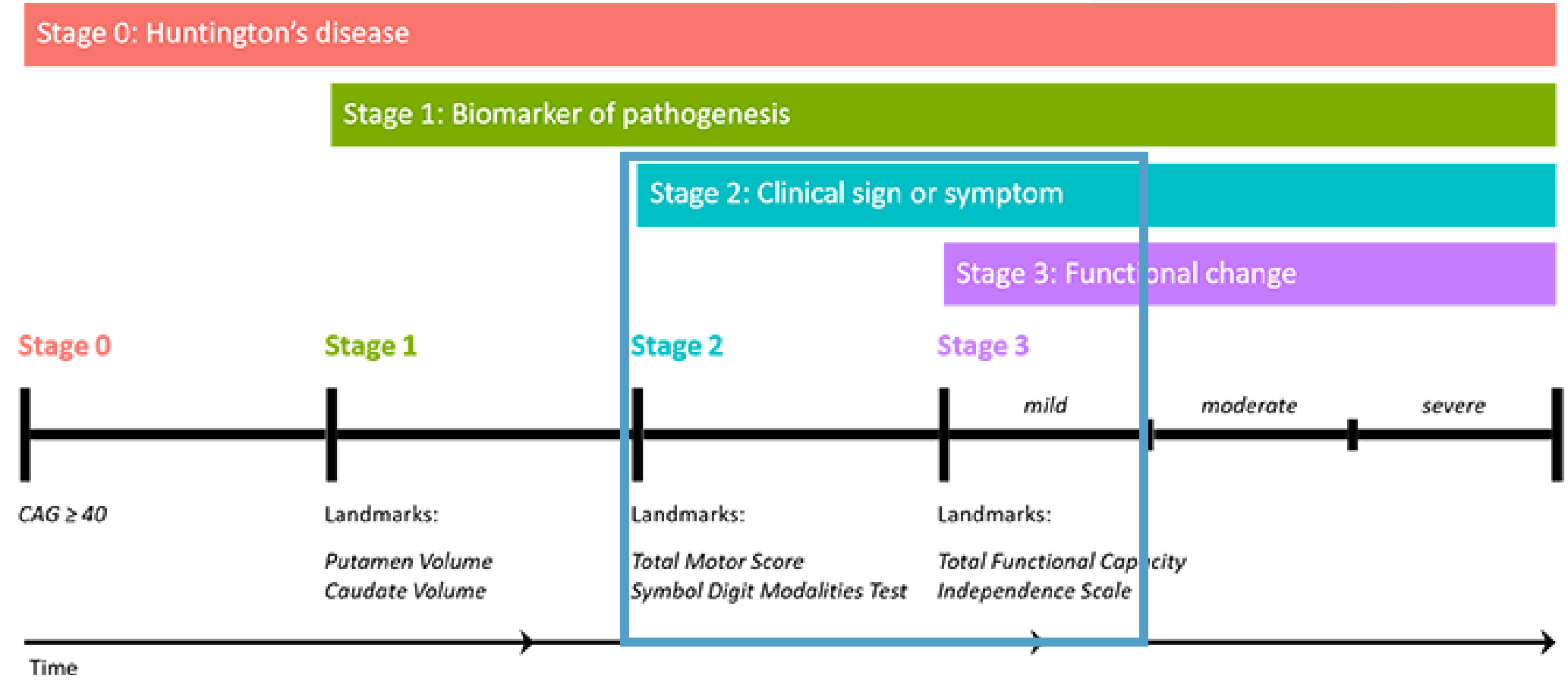
Medication overview for Adult-onset HD

- Motor symptoms:
  - VMAT2 inhibitors
  - Neuroleptics
  - Amantadine

- Psychiatric symptoms:
  - SSRIs or SNRIs
  - Neuroleptics
  - Mood stabilizers

- Cognitive symptoms:
  - Inconclusive or negative results for all cognitive medications
  - Minimize medications with potential cognitive side effects

HD-ISS (integrated staging system)



UniQure (AMT-130)

- Viral vector delivered via brain surgery
  - Low vs high dose vs sham (switch to external control: Enroll-HD)
- Sept 2025: Positive data from Phase I/II trial for high-dose
  - 12 participants with data at 36 months
- 75% slowing of disease progression as measured by cUHDRS
  - Treated patients had a mean change in cUHDRS from baseline of -0.38 compared to -1.52 for controls
- 60% slowing of disease progression as measured by TFC
  - Treated patients had a mean change in TFC from baseline of -0.36 compared to -0.88 for controls

UniQure (AMT-130)

- AMT-130 was generally well-tolerated
  - Most common adverse events due to administration procedure, which resolved.

- Press Release December 3, 2025:
  - "… FDA conveyed that data submitted from the Phase I/II studies of AMT-130 are currently unlikely to provide the primary evidence to support a BLA submission."

- Previously the FDA stated that data from the Phase I/II studies would be sufficient to support accelerated approval
  - UniQure is requesting another meeting with FDA in early 2026

Novartis (Votoplam)

- Oral huntingtin lowering pill
- Completed Phase II PIVOT-HD Trial
  - 5mg vs 10mg vs placebo
- No serious adverse events and favorable safety profile
- Lowered huntingtin protein in the blood at 12 weeks
  - Decreased NfL levels
  - Positive trends in the cUHDRS at 24 months
  - Used Enroll-HD cohort as external control
- Phase III trial planned to start summer 2026

Roche (Tominersen)

- Huntingtin-lowering intrathecal injection
  - Non-selective antisense oligonucleotide (ASO)
    - Binds to wild-type and mutant HTT allele
    - Reduces total huntingtin protein

- Phase II trial, GENERATION-HD2 (n=301)
  - 60mg vs 100mg vs placebo
    - Only continuing with 100mg after IDMC review in April 2025
  - Continues to appear safe and tolerable

- Study completion expected end of 2026

Roche (RG6496)

- Selective ASO, Huntingtin-lowering intrathecal injection
  - Target single nucleotide polymorphism (SNP) on the mutant huntingtin allele
    - Reduces mutant huntingtin protein only
- Estimated 40% of HD population carries the target SNP
- Phase I trial: POINT-HD
  - Planned for 7 months
    - Single dose vs placebo
  - Primary endpoint: Safety and tolerability
  - Study currently open in New Zealand and Australia
    - More sites being planned
    - First participant dosed Dec 2025

Skyhawk Therapeutics (SKY-0515)

- Oral huntingtin-lowering drug
  - Once daily dosing

- Phase I Part C (n=26)
  - 3mg vs 9mg vs placebo
  - No serious side effects
  - Dose-dependent lowering of huntingtin protein seen at 12 weeks (29% vs 62%)
  - Full results expected mid-2026

- Ongoing Phase II/III, FALCON-HD
  - 10 sites across Australia and New Zealand
  - Low vs medium vs high dose vs placebo
  - 12-month treatment period
  - First patient dosed in June 2025

Stem Cells in HD

- Phase II, Randomized double-blind trial
- NestaCell: Human dental pulp stem cells (n=32)
  - Low dose (n=13) vs high dose (n=12) vs placebo (n=7)
  - Nine infusions over 11 months
- Favorable safety profile
- Improvements in UHDRS-TMS in both treatment doses
  - Trend of slower volume loss seen on MRI brain but not significant
- Phase III study not currently recruiting

SOM Biotech (SOM3355)

- Oral beta-blocker that can act as both VMAT1 and VMAT2 inhibitor
- Potential to help motor and mood symptoms

- Phase IIb trial not yet published
  - Received orphan drug status from EMA
  - FDA agreed with Phase III trial plan

- Phase III trial planned to start in late 2026
  - 600mg drug vs placebo x 12 weeks
  - 9-month open label extension

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Questions?