# Updates in Huntington's Disease
# AL Academy of Neurology 2017

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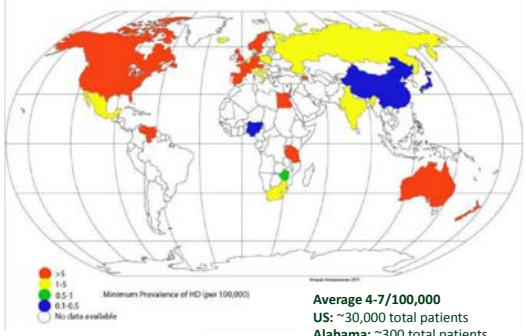
THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

## Updates in HD 2017

- The UAB / HDSA Huntington's Disease Center of Excellence
  - Updates, what are we up to?
  - Genetic testing in HD
- Updates on Symptomatic Treatment Options
- Research for a Cure!

## Worldwide Prevalence of HD




**Average 4-7/100,000**
**US:** ~30,000 total patients
**Alabama:** ~300 total patients
**Mississippi:** ~200 total patients

## Thanks to my Multidisciplinary Team!!
## UAB / HDSA Center of Excellence

## UAB / HDSA Center of Excellence

- Currently following ~185 patients with Huntington's disease
- Monthly multidisciplinary clinic
  - Each patient sees PT, OT, ST, psychiatrist, neurologist, social worker
  - Only my visit is billed, all other care paid through CoE grant


## Updates on Diagnosis of HD

- Traditional: chorea (or other HD symptom) plus consideration of family history then confirmation by gene test
- 3 patients this year with chorea, no FHx of HD, age >75, gene test positive for HD
- When/how to get the gene test?
  - Symptomatic testing
    - Simple in-office counseling, then direct order of gene test
    - UAB does NOT perform gene test so must use outside lab
    - Not covered by Medicare or Medicaid
    - Athena: $1200; Baylor: $450; Emory: $400 ($300 with UAB discount)

## Updates on Diagnosis of HD

- Presymptomatic testing
  - Despite availability, only 5% of those at-risk choose to test
  - UAB HD Clinic offers:
    - FREE initial genetic counseling by phone
    - Anonymous and FREE neurology evaluation
    - Only cost to the patient is gene test itself
      - Can test under a pseudonym if patients prefer
    - To access this, please DO NOT refer the patient via usual vehicles but instead call our clinic directly (205-996-2807) and we will set this up for the patient!

## Clinical Presentation of HD

- Average age of symptom onset is 30's-50's
  - Socioeconomic impact of loss of prime productivity years
  - By then, many have had children
- Loose correlation of CAG repeat length and symptom onset/severity

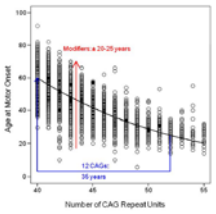
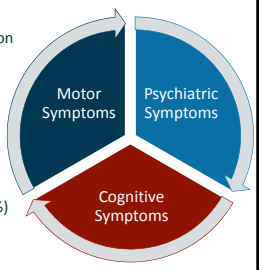



FIG. 1. The relationship between CAG and age at motor onset and effects of modifiers. Age at onset of diagnostic motor signs (Y-axis) are plotted against *HTT* CAG repeat length (X-axis). Black line represents a statistical model relating the relationship between age at onset and CAG repeat length-based quality control passed data. Black circles represent HD homozygote individuals plotted based on the longer of their two expanded *HTT* CAG tracts. For comparison, the blue lines indicate that 12 CAG units make a difference of 35 years in mean age at onset, whereas the red line indicates that at a single repeat length, there is the potential for naturally occurring genetic modifiers to delay onset by 20 to 25 years later than the mean.

Gusella, et al 2014

## Clinical Presentation - "HD Triad"

- Motor
  - Most common (90%) is **chorea** – effects on gait, coordination, speech, swallowing
  - Can also consist of tics, dystonia
  - Slowing of smooth pursuit/saccades
- Cognitive
  - Executive dysfunction progressing to full dementia
- Psychiatric/Behavioral
  - Most common: Depression/OCD (30-80%)
  - Impulsivity and Suicide risk
  - Irritability, Apathy, Personality change



## Updates on Symptomatic Treatment of HD

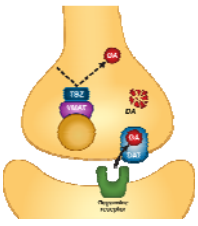
- No cure but myth of "nothing we can do"
- Symptomatic Therapy
  - Chorea:
    - Deutetrabenazine (Austedo) – FDA approved 4/2017
    - Tetrabenazine (Xenazine) – FDA-approved 2007
      - Now generic, 3 makers, still primarily specialty pharmacy, gross cost is $90,000/year (branded Xenazine was $120,000/year)
    - Typical and atypical (not quetiapine/clozapine) antipsychotics – off-label, very little data
    - Amantadine - Used by some, but very little data
    - Benzodiazepines - Again, limited data; Can worsen gait/falls
    - DBS – a few case-series, have not done this yet at UAB

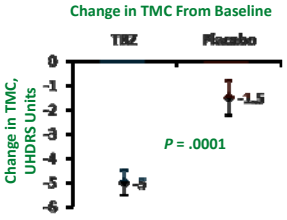
## Updates on Symptomatic Treatment of HD

- Other Non-Motor Symptoms
  - Depression/Anxiety: often responds even better to SSRI's/SNRI's, etc. than traditional depression
  - Perseveration/Impulsivity/Irritability: Mood stabilizers (valproate, oxcarbazepine)
  - Delusions: Typical or atypical antipsychotics
  - Cognition: *No proven pharmacotherapies*, so **no** utility for cholinesterase inhibitors or memantine (all studied and failed)

## Tetrabenazine for HD

- VMAT-2 Inhibitor, FDA approved for HD chorea




Huntington Study Group. *Neurology*. 2006;66:366-372.

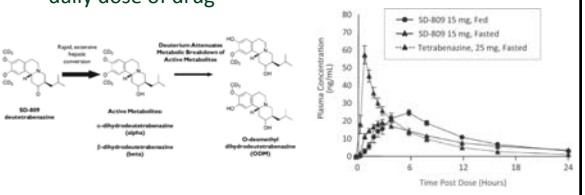
## Tetrabenazine for HD

- Symptomatically suppresses chorea of all etiologies
- My success stories
- Can have problematic side effects
  - Increased bradykinesia/parkinsonism
  - Sedation
  - Akathisia
  - Depression

Adam OR, Jankovic J. *Neurotherapeutics*. 2008;5:181-97.
Kenney C, Jankovic J. *Expert Rev Neurother*. 2006;6:7-17.

## Deutetrabenazine for HD

- Deuterium-substituted tetrabenazine changes PK profile, allows similar efficacy with less (50%) total daily dose of drug




## Deutetrabenazine vs. TBZ

- Caveat – NOT a head-to-head study, but…

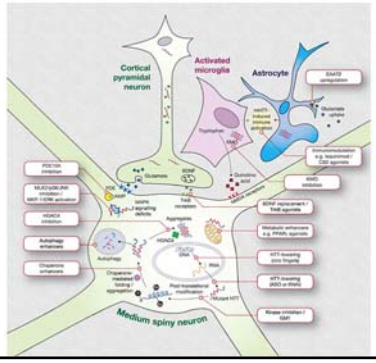
| | FIRST-HD | | | TETRA-HD (Study 004) | | |
|---|---|---|---|---|---|---|
| | SD-809, n=45 | Placebo, n=45 | p-value | TBZ, n=54 | Placebo, n=30 | p-value |
| **Efficacy** | | | | | | |
| Total Maximal Chorea Score (TMC) Primary endpoint | 4.4 | 1.9 | <0.0001 | 5.04 | 1.52 | <0.0001 |
| Total Motor Score (TMS) | 7.4 | 3.4 | 0.002 | 6.84 | 3.51 | 0.0752 |
| **Safety - Select Adverse Events** | | | | | | |
| Sedation/somnolence | 5 (11.1%) | 2 (4.4%) | - | 17 (31%) | 1 (3%) | - |
| Insomnia | 3 (6.7%) | 2 (4.4%) | - | 12 (22%) | - | - |
| Depression/Agitated Depression | 2 (4.4%) | 3 (6.7%) | - | 10 (19%) | - | - |
| Anxiety | 1 (2.2%) | 1 (2.2%) | - | 8 (15%) | 1 (3%) | - |
| Irritability | 3 (6.7%) | 6 (13.3%) | - | 5 (9%) | 1 (3%) | - |
| Akathisia | 1 (2.2%) | 1 (2.2%) | - | 10 (19%) | - | - |
| Nausea | 1 (2.2%) | 2 (4.4%) | - | 7 (13%) | 2 (7%) | - |
| Vomiting | - | 3 (6.7%) | - | 3 (6%) | 1 (3%) | - |
| Fatigue | 3 (6.7%) | 2 (4.4%) | - | 12 (22%) | 4 (13%) | - |
| Fall | 2 (4%) | 4 (9%) | - | 8 (15%) | 4 (13%) | - |
| Upper respiratory tract infection | - | 1 (2%) | - | 6 (11%) | 2 (7%) | - |

TMC and TMS are subscales of the Unified Huntington's Disease Rating Scale (UHDRS)

## Logistics of Ordering TBZ and Austedo

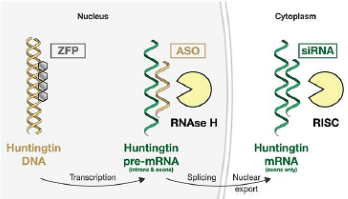
- How to order tetrabenazine now that it has gone generic?
  - TAGI pharmaceuticals through variety of different pharmacies (QuickRx)
- PSR Form for Austedo
  - https://www.austedo.com/renderpdf.aspx?file=PSR_Form.pdf
- What about for inpatients?

## Current Scientific Approaches – Search for a Cure

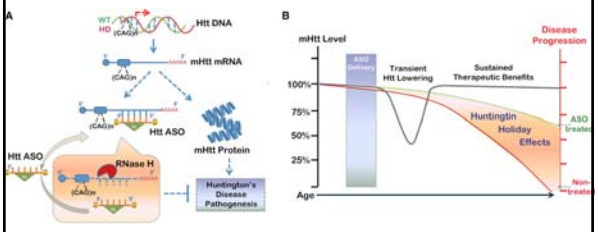



## Gene Silencing

- In mice, switching off *mHtt* allows recovery of neurons
- Gene silencing technologies (goal is lowering *mHtt* expression)
  - Zinc finger proteins (ZFP)
  - Small interfering RNA (siRNA)
  - Antisense oligonucleotides (ASO)



## AntiSense Oligonucleotides




Lu and Yang 2012

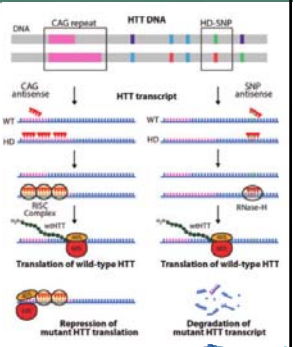
## Antisense Oligonucleotides

- Phase1b **safety** study began late 2015!! (Ionis-HttRx)
- Efficacy of ASO will NOT be determined in this trial
- Ionis-HttRx is an ASO that lowers normal and mutant *huntingtin*
- Duration of action ~ 4months
- Drug to be delivered intrathecally
- Due to complete Sept. 2017
  - No major safety events thus far…

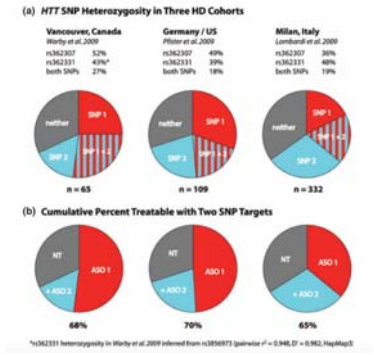
36 patients + placebo controls
4 doses (10, 30, 50 and 70 mg)
14 week study at clinical sites in UK, Germany and Canada only
Post-treatment observation up to 29 weeks

## WAVE LifeScience ASO

- WSE-120101 will be an ASO that targets the single nuclear polymorphism (SNP) rs362307
- Attempt to be allele-specific silencing



## WAVE LifeScience ASO




## WAVE LifeScience ASO

- Similar to Ionis-HTTRx, will require infusion via spinal tap
- Small initial study (Mass. General, Vanderbilt, Johns Hopkins) for safety to commence late 2017
- Subjects will first have SNP sequenced, and based on presence of SNP 1, 2, or both, will be entered into appropriate study.
- ~60-75% of HD patients should be eligible

## Gene Editing: Zinc Finger Proteins/CRISPR

- ZFN's create double stranded breaks in DNA at specific points
  - Requires creation of custom targeted DNA sequence
- Clustered regularly interspaced short palindromic repeats (CRISPR)
  - Combines existing defense mechanism against viral invasion with RNA guide to target and excise DNA sequences (ie could shorten a 42 to a 22)
- uniQure developing AAV5-miRNA model to knockdown mHtt production
  - Would require only single dose

## Gene Silencing Challenges

- Delivery and Distribution
  - Since treatments do not cross BBB into the brain, how to deliver?
  - Even delivered directly into CNS, hard to get into areas most affected by HD
- Allele-selective silencing
  - What are effects of suppressing normal Htt?
  - How to just turn off the mHtt but leave normal Htt on?
- Side effects?
- Which patients to treat?

## Take Home Message

- HD is a difficult disease due to its inheritance pattern and ability to devastate entire families
- BUT there is hope
  - Treatments (that really work) NOW
  - Exciting things on the horizon…
- Annual HD Education Day, UAB Alumni House, 9/16/17
- Send us your HD patients!!
  Jenna Smith, RN, Clinic Coordinator: **205-996-2807**