

Neuropsychiatry of Tourette Syndrome & Tic Spectrum Disorders

Jeremiah Scharf, M.D., Ph.D.

Division of Cognitive and Behavioral Neurology
Center for Brain-Mind Medicine
Brigham and Women's Hospital

Psychiatric Neurodevelopmental Genetics Unit
Tic Disorders Unit
Division of Movement Disorders
Massachusetts General Hospital

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Disclosure of Potential Conflicts

Source	Consultant	Advisory Board	Stock Equity >\$10,000	Speakers Bureau	Research Support	Honorarium	Travel Support
Tourette Association of America		X			X		X
TLC Foundation for Body-Focused Repetitive Behaviors		X			X		X
National Institutes of Mental Health					X		
National Institutes of Neurological Disorders and Stroke					X		

- *Neither I nor my spouse has a relevant financial relationship with a commercial interest to disclose.*
- *Off label indications will be discussed.*

Learning Objectives

At the conclusion of this activity, the participant should be able to:

- Explain the current diagnostic criteria for various tic disorders and their limitations
- Describe the epidemiology, natural history and presumed pathophysiology of tic disorders
- Describe the common co-occurring neuro-psychiatric conditions associated with tic disorders
- Discuss pharmacological and non-pharmacological treatment options for tic disorders

What are tics?

- Rapid, arrhythmic, stereotyped movements
- Most commonly involve head, neck and arms
- Occur in bouts
- Tend to wax and wane over time
- Usually are partially suppressible
- Often preceded by a premonitory urge/itch/tension
- Separated clinically into different types:
 - motor vs. vocal
 - simple vs. complex

Tics



**“I Have Tourette’s But Tourette’s Doesn’t Have Me”,
HBO, courtesy of the Tourette Association of America**



Simple Tics

- **Brief contractions of isolated muscle groups**

Motor

- Sniffing
- Coughing
- Throat clearing
- Grunting
- Barking/animal sounds

Vocal

- Eye blinks
- Nose twitches
- Grimaces
- Shoulder shrugs
- Head, arm or leg jerks

- Simple vocal tics are **just contractions of pharyngeal, laryngeal or respiratory muscles** resulting in sounds*





Complex Tics

Motor

- Coordinated movements of multiple muscle groups
- May appear slower and “purposeful”
- Complex Gestures/Postures
- Echopraxia (mirroring others' movements)
- Poking/pinching/punching (aggressive, self-injurious)
- Touching/tapping/picking (compulsive)

Vocal

- Complex utterances
- Syllables
- Words
- Phrases
- Echolalia (repeating others)
- Palilalia (repeating oneself)
- Coprolalia (socially inappropriate)
 - Present in **ONLY 10-20%** of TS patients



Spectrum of Developmental Tic Disorders

- Transient Tic Disorder (TTD)
 - Single or multiple tics lasting > 4 weeks, < 1 year
 - Now “Provisional Tic Disorder” in DSM-5

- Chronic (Persistent) Motor (or Vocal) Tic Disorder (CTD/PTD)
 - Multiple motor OR vocal tics lasting > 1 year
- Gilles de la Tourette Syndrome (GTS/TS)
 - Multiple motor AND one vocal tic lasting > 1 year
 - Onset before age 18
 - **MISCONCEPTION:** Patients must have verbal tics (i.e., words) to have TS.

Continuous biological
spectrum





Epidemiology of TS/PTD

- Population prevalence estimates vary widely
- Recent community-based estimates:
 - Transient Tics: **25%**
 - TS: 0.5-1% (higher in special education populations)
 - Chronic (Persistent) Tic Disorder: **1-2%**
- 4:1 male:female ratio for TS; 2:1 for CTD/PTD

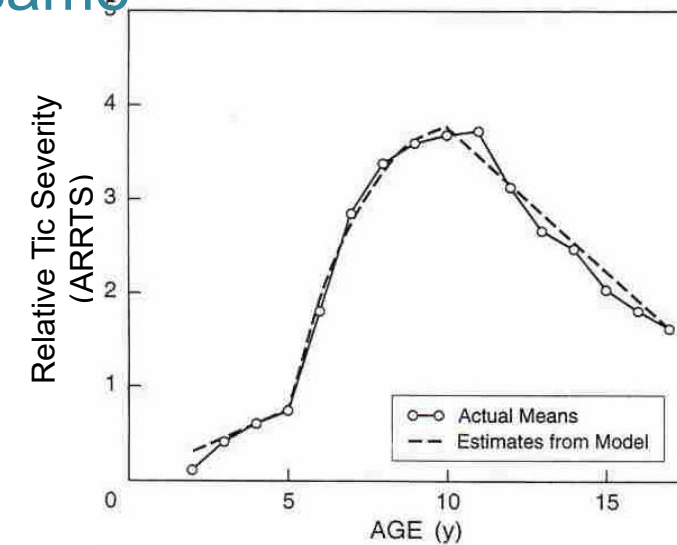
<https://www.cdc.gov/ncbddd/tourette>





Epidemiology of TS/PTD

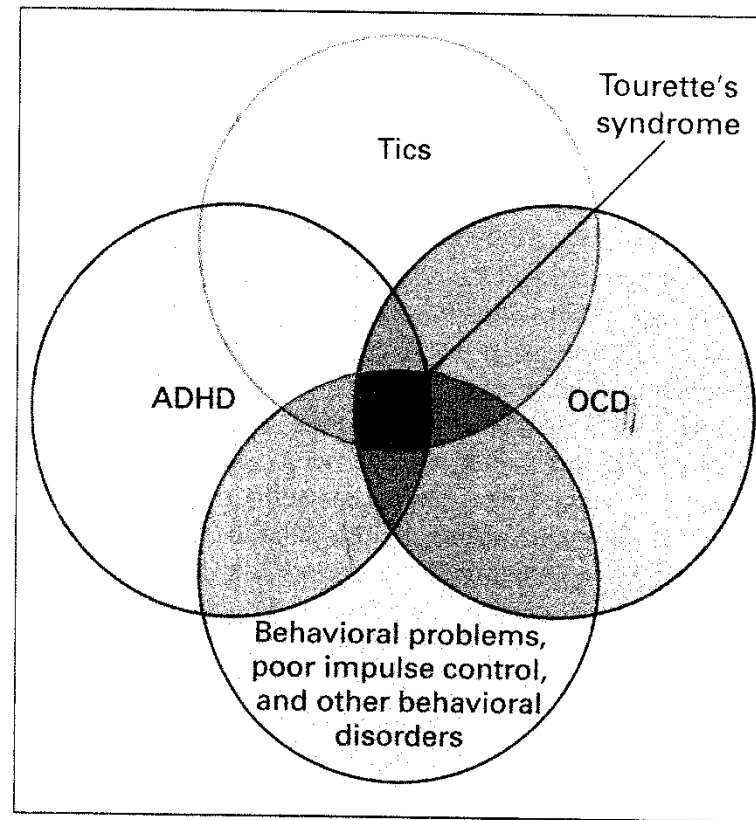
- Mean age of onset is age 5 to 7
- Maximum severity typically in early adolescence
- Most improve in late adolescence/early adulthood
 - **'Rule of Thirds'**: 1/3 resolve, 1/3 improve, 1/3 stay the same
 - Rough estimate
- Follow-up study of 227 patients from TS clinic
 - 20% of pts >age 16 had no tics
 - 60% had minimal or mild tics
 - **20% had moderate-to-severe tics**
- Swedish national registry database
 - **20% of children diagnosed with TS are still seen as adults**





TS Co-occurring Disorders

- Approximately **85% of TS clinic patients** have 1 or more additional neuropsychiatric disorders
- **Co-occurring disorders are often more disabling than tics!!!**



Obsessive Compulsive Disorder (OCD)

- **Obsessions:** recurrent, intrusive thoughts/images
 - Thoughts produce intense distress and anxiety
 - Examples: Contamination, ordering/ arranging, symmetry, aggressive/sexual/religious thoughts, etc.
- **Compulsions:** Rituals used to neutralize obsessions
 - “Repetitive behaviors” or mental acts that must be performed in response to obsession or with rigid rules
 - Performance causes temporary relief of anxiety
 - Examples: Cleaning/washing, checking, ordering, counting, repeating, praying, evening up, etc.
- Symptoms waste time or cause distress/impairment

Epidemiology of OCD

- Two peaks of onset
- Adult onset: Age 20s-30s, female predominant
- Childhood onset: Age 6-18, male predominant
 - Childhood-onset with tics
 - Childhood-onset without tics
- Waxing-waning course
- Exacerbated by stress, fatigue, illness
- Symptoms thought to persist throughout adulthood**
 - **BUT: Only ~40%** of TS patients with OCD at age 12 had OCD when re-assessed at age 16+



TS and OCD

- 30-60% of TS patients meet DSM-5 criteria for OCD
 - Even more have subclinical OC behaviors
- Most TS patients report a premonitory sensory “urge”/ tension relieved by performance of tic
 - Sensorimotor equivalent of OC urge/response?
- Many complex tics have compulsive features (“evening up”, “just right” phenomena)
 - **Treatment implications:** Compulsive tics often require tic” and “OCD” treatments to improve symptoms





TS and ADHD

- 60-90% of TS pts have co-occurring ADHD
- Tic disorders are more frequent in children with ADHD than in children without ADHD
- TS+ADHD is associated with:
 - Increased tic severity
 - Increased impairment
 - Additional co-occurring disorders
 - oppositional defiant disorder
 - intermittent explosive disorder (“rage”)
- **TS/OCD/ADHD co-occurrence: ~30-50% of TS pts**





Additional Neuropsychiatric Disorders in Patients with TS/PTD

- Impulse dyscontrol/"rage" attacks: **15-30%** of pts
- Anxiety and mood disorders: **~40%**
- Self-injurious behavior: **~15%**
- Sleep disorders: **25-50%**
- Learning disabilities: **~25%**
- Autism spectrum disorders: **10-20%**
- When seeing a patient with TS/PTD, **screening for co-occurring conditions** is often more important than treating the tics!

****AAN Guideline****



Tourette Syndrome: Pathophysiology

- TS is a biological, neuropsychiatric disorder under the influence of the external environment
- Studies implicate abnormal development of circuits between the ***basal ganglia, thalamus and cerebral [frontal] cortex***
- Pharmacology:
 - Altered dopamine (DA) function, though inconsistent
 - DA transport/release/binding abnormalities not reported
- Imaging
 - Decreased basal ganglia volumes on CT/MRI (~2-3% Δ)
 - Altered functional activity in frontal-striatal-thalamic circuits
 - Impaired **top-down control** of motor circuits
- Autopsy studies
 - altered density & number of GABA+, parvalbumin+ inhibitory inter-neurons and cholinergic neurons in the basal ganglia

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Cortico-striato-thalamo-cortical (CSTC) circuits implicated in TS, OCD & ADHD

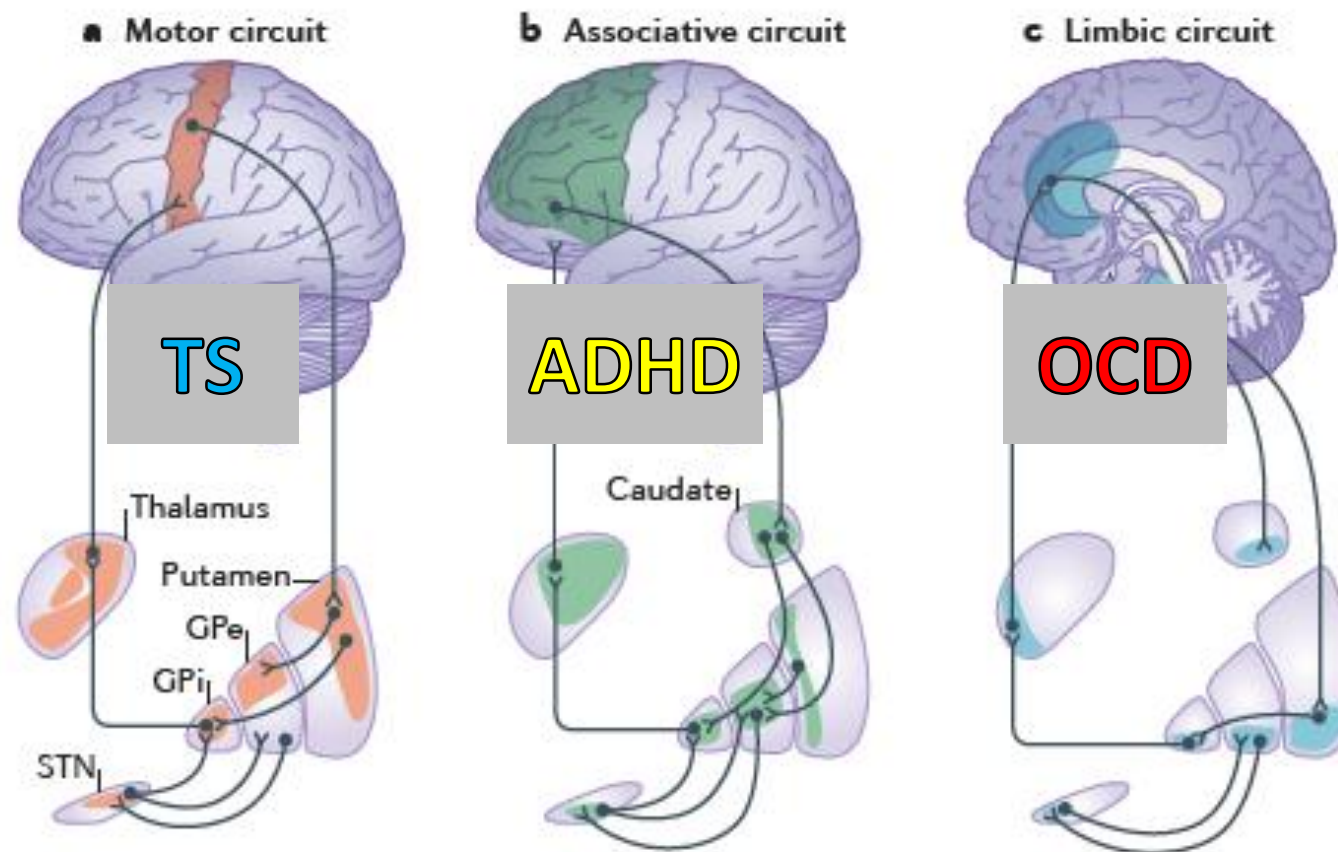


Figure 1 | The main functional subdivisions in the sensorimotor, associative and limbic cortico-striatal circuits. The striatum (which comprises the caudate and the





TS/PTD has complex genetic underpinnings

- Relatives of TS patients have increased risk of:
 - **TS**: 10-20%
 - Persistent Vocal or Motor Tics (PMVT): additional 10-20%
 - **OCD**: 10-20%
- Twin studies support TS/PMVT genetic component
 - Heritability estimates ~80-90%
 - Suggests both genetic and non-genetic risk factors
- Data indicate TS is highly polygenic (i.e., like height)
- Definitive TS genes are starting to be identified
 - *NRXN1* deletions, *CNTN6* duplications, *CELSR3* mutations





Differential Diagnosis of Tics

- **Tic “mimickers”**
 - **Allergies**
 - **Complex Motor Stereotypies*** [colloquially known as “**stimming**” or “**flapping**”]
 - Bilateral hand movements; onset < age 3
 - Persistent, rhythmic, repeated continuously at expense of other intended movements [typically bilateral pronation/supination or flexion/ extension of both hands and arms]
- **Tic disorders**
 - **Primary developmental tic disorder (TS/PTD)**
 - **Secondary tic disorder from basal ganglia injury** (almost **always** w/ other movements)
 - **Drug-induced movement disorders**
 - Trauma, vascular (stroke/hemorrhage), toxins, infections (encephalitis)
 - Autoimmune disorders (lupus, antiphospholipid syndrome)
 - Rare inherited basal ganglia disorders (Wilson disease, Huntington dz)



Complex Motor Stereotypies

From EM Mahone et al., J. Pediatrics, 2004



TS: Diagnostic Evaluation

- Diagnosis made primarily on history
 - Key is observations from multiple historians
- ***Screen for neuropsychiatric co-morbidities***
- Assessment of impairment/distress
 - Family, friends, school, work
- Neurological examination usually normal
- No routine labs or imaging are necessary unless history is atypical or exam is abnormal



TS Treatment Overview



Practice Guideline: The Treatment of Tics in People with Tourette Syndrome and Chronic Tic Disorders

AAN Practice Guidelines: Treatment of Tics in ... TS and CTDs. *Neurology*, 2019

Report by:

Guideline Development, Dissemination, and Implementation Subcommittee of
the American Academy of Neurology

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Slide 1

TS Treatment Overview

- Most children don't need tic treatment
Watchful waiting is appropriate if tics are not causing physical, psychological, or educational impairment.
- Treatment should only be considered if tics cause *significant distress and/or impairment*
- Identify/treat most problematic target symptoms first
- Treatments include pharmacological, behavioral or combined interventions.

AAN Practice Guidelines: Treatment of Tics in TS and CTDs. *Neurology*, 2019



TS: Non-pharmacological Treatment

- CBIT (**C**omprehensive **B**ehavioral **I**ntervention - **T**ics)
 - Functional Analysis
 - » Identify patient-specific antecedent events (tic triggers) and potentially reinforcing consequences
 - » Identify social situations that influence behaviors
 - Function-based Intervention of External Factors
 - » Intervene to remove or minimize triggers or consequences
 - HRT (**H**abit **R**eversal **T**raining)
 - » Awareness Training
 - » Competing Response
 - » Social Support

****AAN Guideline**

CBIT/HRT was more effective than supportive therapy in two RCTs

****CBIT/HRT is now considered first-line treatment for TS/Tics****





CBIT/HRT – Competing Response

- Opposite to or incompatible with the tic movement
 - Motor: Isometric muscle tensing
 - Vocal: Slow rhythmic deep breathing through nose with mouth closed
- Capable of being maintained for a brief period of time (~ 1 minute)
- Socially inconspicuous
- Compatible with normal ongoing activities



Goals of CBIT/HRT

- Harness brain systems to mitigate symptoms
 - Not about “voluntary control”
 - Learning a management strategy
- Empower patients to do something about their tics
- Help patients feel more in control
- Stress management reduction
- **Two recent controlled clinical trials also demonstrated efficacy for internet-guided CBIT for tics.**



TS Pharmacotherapy Overview

- Three “tiers” of tic medications
 - **Tier 1: Alpha-2 agonists (clonidine, guanfacine)**
 - Fewest side effects; generally small effects
 - Good for mild tics
 - **Tier 2: Atypical neuroleptics w/ high D2 receptor potency (risperidone, ziprasidone, aripiprazole, etc.)**
 - Aripiprazole is FDA approved for TS
 - Medium range side effects – but still can cause Tardive dyskinesia!
 - **Tier 3: Typical neuroleptics w/ highest D2R potency (haloperidol, pimozide, fluphenazine)**
 - Haloperidol and pimozide are FDA-approved for TS
 - Often needed for severe tics
 - Generally 3rd line agents due to side effect risk profile





TS Pharmacotherapy: Mild-moderate tics

Alpha-2 agonists

- Clonidine (Catapres) and guanfacine (Tenex, Intuniv)
 - ***Clonidine has been used for >20 years to treat TS***
 - reduces both motor and vocal tics
 - reduces ADHD symptoms (disinhibition, impulsivity, hyperarousal, and motoric overactivity)
 - tends to work best for individuals with TS/Tics and ADHD
- Neither as effective for inattention as stimulants
- Guanfacine is usually less sedating and longer acting
 - Clonidine dosed **tid-qid** in children; **bid** in adolescents/adults
 - Consider clonidine patch (less sedating; local skin reaction in ~25%)
 - Guanfacine (generic) is dosed **bid** in adolescents & adults
 - Guanfacine ER formulation may not work as well as immediate release





TS Pharmacotherapy: Moderate-severe tics

Atypical Dopamine D2 receptor antagonists (aka, neuroleptics)

- Atypical neuroleptics studied in Tourette Syndrome
 - risperidone (Risperdal)
 - aripiprazole (Abilify) – FDA approved for TS in adults & children
 - ziprasidone (Geodon) [less weight gain, but requires EKG QTc monitoring]
- Anti-tic efficacy correlates directly with dopamine D2 receptor blocking activity (risperidone > ziprasidone > olanzapine)
- Doses are relatively low compared to those used in other psychiatric disorders
 - **NOTE: Any dopamine D2 receptor antagonist can cause tardive dyskinesia!!!**
- Due to potential side effects, careful medical evaluation prior to treatment and ongoing monitoring is essential;
- For risperidone, start 0.125-0.25 mg daily
- Target dose: Total daily dose 0.5-3 mg daily in divided doses





Atypical Neuroleptics: Monitoring

- Serum chemistries, Liver Function Tests, Complete Blood Count (CBC) prior to initiation
- EKG prior to initiation (particularly ziprasidone)
- Weight, waist circumference, BMI: outset & followups
 - Consider use of metformin in pts w/ high baseline BMI
- Fasting glucose and lipid profiles: at outset & q3-6 mos.
- Neurologic monitoring for motor side effects
- *Take home point: Use if necessary, but serial monitoring is required for longer term use.*





TS Pharmacotherapy: Severe tics

Typical neuroleptics

- FDA approved medications for TS
 - Haloperidol (Haldol)
 - Pimozide (Orap)
 - **NOT** clearly better than haloperidol or other high potency dopamine D2 receptor antagonists
 - Has many drug-drug interactions plus requires EKG monitoring for QTc prolongation
 - Fluphenazine (Prolixin): commonly used; not FDA approved
- Most effective class of tic medications
- Side effect profiles are NOT favorable:
 - Tardive dyskinesia (NOTE: atypical neuroleptics can also cause tardive dyskinesia)
 - Extrapyrarnidal (motor) side effects: Parkinsonism, akathisia, tremors
 - Weight gain
 - Sedation and cognitive dulling

****AAN Guideline****





Additional Tic Reduction Medications

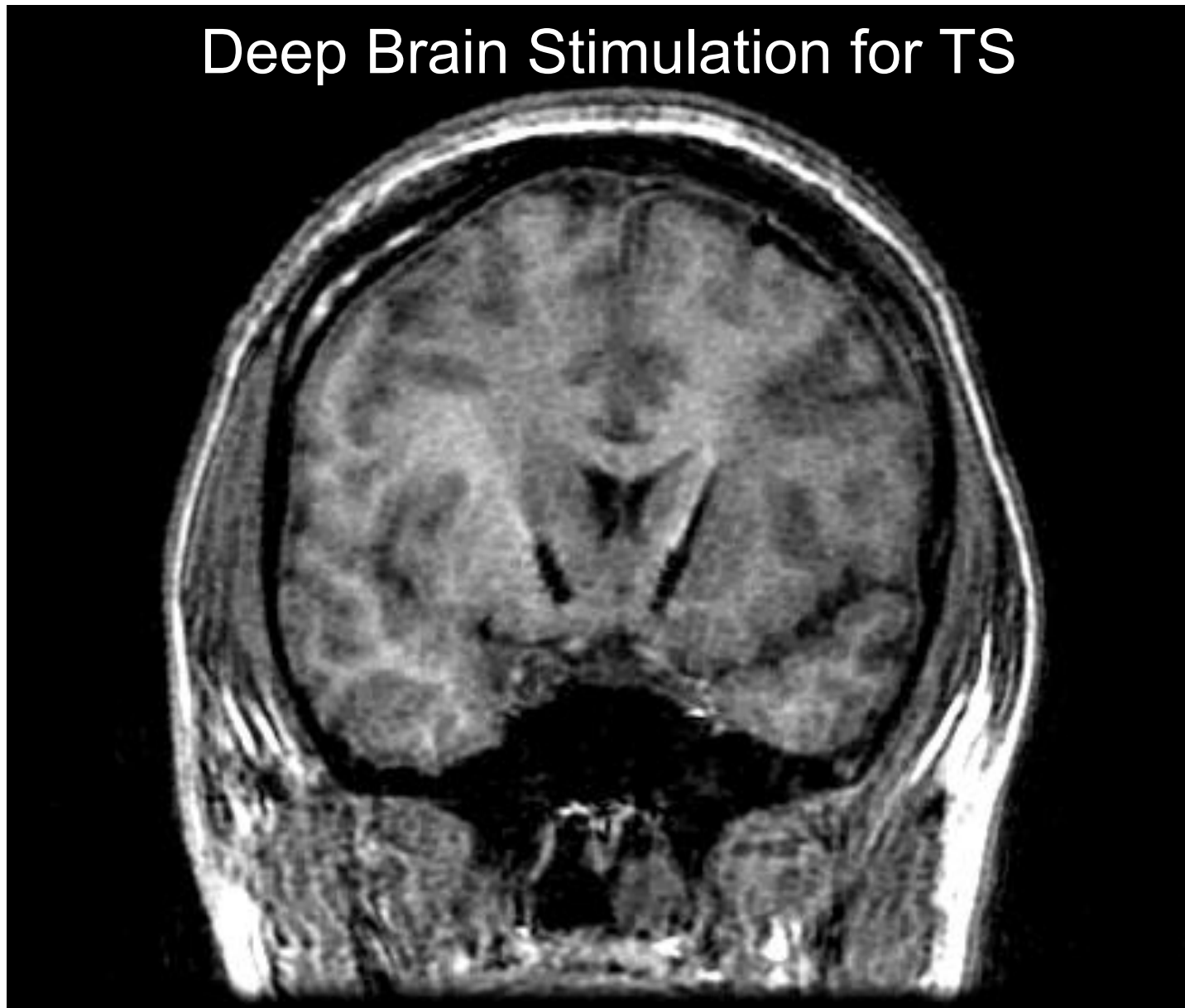
- **Benzodiazepines:** Clonazepam
- **Topiramate:** (+/-); minimal clinical trial evidence
- **Baclofen (GABA modulator):** (+/-); minimal clinical trial evidence
- **Tetrabenazine (Xenazine):** effective, but is expensive & can precipitate depression in 25% of patients
- **Tetrahydrocannabinol (THC):** mixed results; blinded studies confounded by psychoactive effects on drug
- **Botulinum toxin injections**

Currently in randomized controlled clinical trials:

- **Ecopipam – D₁R antagonist** – currently submitted for FDA review
- **Gemlapodect – PDE10A inhibitor** – blocks dopamine D2 Receptor signaling
- **Nindong Granule (Zhao formulation)** – traditional Chinese medicine; multiple RCTs in China; existing plans to conduct randomized controlled trials in the US



Deep Brain Stimulation for TS





Deep Brain Stimulation in TS

- Many different sites explored
 - GPi, STN, Centromedian thalamus, anterior limb of the internal capsule
- Largest cohort (open label) is 36 pts with bilateral centromedian-parafascicular nucleus (Cm-Pf) thalamic stimulation
 - 15 patients had sustained improvement at 2 years, but still symptomatic
 - 3 with “less satisfactory” responses; dropped out prior to the 2 year endpoint
 - High rates of complications (35%)
 - **Higher complication rate than seen for DBS in other disorders**
- Unclear how DBS affects TS co-occurring neuropsychiatric conditions
- ****Controlled clinical trials are needed to determine efficacy****
 - 1 Class II study of 16 patients (anterior GPi): negative results at 3m

****AAN Guideline****





OCD Treatment in TS: Serotonin Reuptake Inhibitors

- Higher doses of SSRIs are needed to treat OCD compared to MDD
 - Caution: FDA warning when using citalopram at doses >40 mg/d (↑QTc)
- OCD with tics is generally harder to treat than OCD without tics
- Augmentation with atypical neuroleptics may be needed
- Tics may transiently worsen with initiation of SSRI
- **Cognitive Behavioral Therapy (CBT)** is very effective and still considered to be first line treatment where available





TS and ADHD Pharmacotherapy

- Clonidine or guanfacine can be helpful if ADHD is mild, and tics are problematic
 - **Good for hyperactivity/impulsivity**
 - **Less effective for inattention**
- Atomoxetine is relatively “tic neutral”, but **not** as effective for co-occurring ADHD as stimulants; no studies of viloxazine effects on tics
- Stimulant use in patients with tics traditionally avoided due to concerns about tic worsening, **but data indicate that many TS patients can tolerate stimulants** with low initial doses, slow titration, **and co-administration with clonidine.**

****AAN Guideline****





TS Summary

- TS is a common biological disorder with both neurologic and psychiatric features
- **TS rarely is an isolated tic disorder**
 - “Hidden” co-occurring psychiatric conditions are often more impairing than overt tics – **and can contribute to tic worsening**
- Many patients need no pharmacological treatment
- **CBIT/HRT** (behavioral therapy for tics) demonstrated efficacy in two multi-center RCTs vs. supportive psychotherapy & recommended as first line treatment by AAN & JAACAP where available





TS Summary

- Clonidine or guanfacine recommended as first tier medication for tics especially for individuals with co-occurring ADHD
- Atypical or typical neuroleptics (dopamine D2 receptor antagonists) should be reserved for severe tics, used cautiously & monitored closely
- Co-occurring disorders should be aggressively sought out and treated, especially in treatment-refractory cases
- For TS+ ADHD, **stimulants are *NOT* contraindicated**, and may be first line treatment if ADHD symptoms are causing impairment
- Ultimate goal is to help patients develop and maintain appropriate self-esteem and coping skills



Acknowledgments

- Tourette Association of America (TAA)

<http://www.tourette.org>

Information about research or participation in TS clinical research/
genetic studies:

<http://scharflab.org>

Questions? Email: jscharf@mgb.org