

# Tic Disorders and Tourette Syndrome

## Diagnosis and management

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Bresnan Child Neurology Course

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# Disclosures

- I have no financial conflicts
- I will be discussing off-label use of medications for tic disorder and Tourette syndrome

# Objectives

- Overview of different tic disorders
- Common comorbidities
- Current pharmacologic treatment options
- Overview of recent American Academy of Neurology guidelines to evidence-based treatment consideration
- Non-pharmacologic treatment options
- What is new on the horizon?

# History of tic disorders

George Gilles de la Tourette was Charcot's intern

- Seprenger, Heinrich (1498)
- William Drake (1663)
- Itard (1825)
- Trousseau (1875)
- Gilles de la Tourette (1885) in *Archives de Neurologie* described 9 patients with "maladie des tics"
- Haloperidol for tics  
Europe (1961), USA (1965)
- DSM-3-R in 1980 (American Psychiatric Association)



*Une leçon Clinique à la Salpêtrière, Brouillet, 1887, Paris*

# Tics

- A tic is a sudden, recurrent, involuntary, nonrhythmic movement or vocalization
- May occur many times a day, nearly every day
- Wax and wane in time, intensity and type of tic



# Tics

## Motor Tics

### SIMPLE

- Eye blinking
- Eye movements
- Nose movements
- Shoulder shrug
- Abdominal tensing

### COMPLEX

- Facial movements
- Head gestures
- Shoulder movement
- Bending or gyrating
- Echopraxia (mimicking other's actions)

## Vocal Tics

### SIMPLE

- Throat clearing
- Coughing
- Sniffing
- Grunting

### COMPLEX

- Syllables
- Coprolalia (obscene words)
- Echolalia (repeating others' words)
- Palilalia (repeating one own's words or phrases)
- Disinhibited speech

# Types of tic disorders

- There are three types of tic disorders (DSM-V):
  - **provisional tic disorder** (<12 months of duration)
  - **chronic tic disorder** (chronic vocal, or chronic motor tics without a tic-free period of more than 3 consecutive months)
  - **Tourette syndrome (TS):**
    - multiple motor tics
    - at least one vocal tic
    - age of onset before age 18
    - duration greater than 1 year
    - not due to a direct physiological effect of medication or medical condition (e.g. post viral encephalitis)



# Prevalence

- Tics are common, occurring in 3-5% of children
- 1 of every 162 children (0.6%) have Tourette Syndrome (TS)
- Boys are three to five times more likely to have TS than girls.

<https://www.cdc.gov/ncbddd/tourette/data.html>, Tourette.org  
Roberts, Lancet Psychiatry, (2015)



# Tip of an iceberg

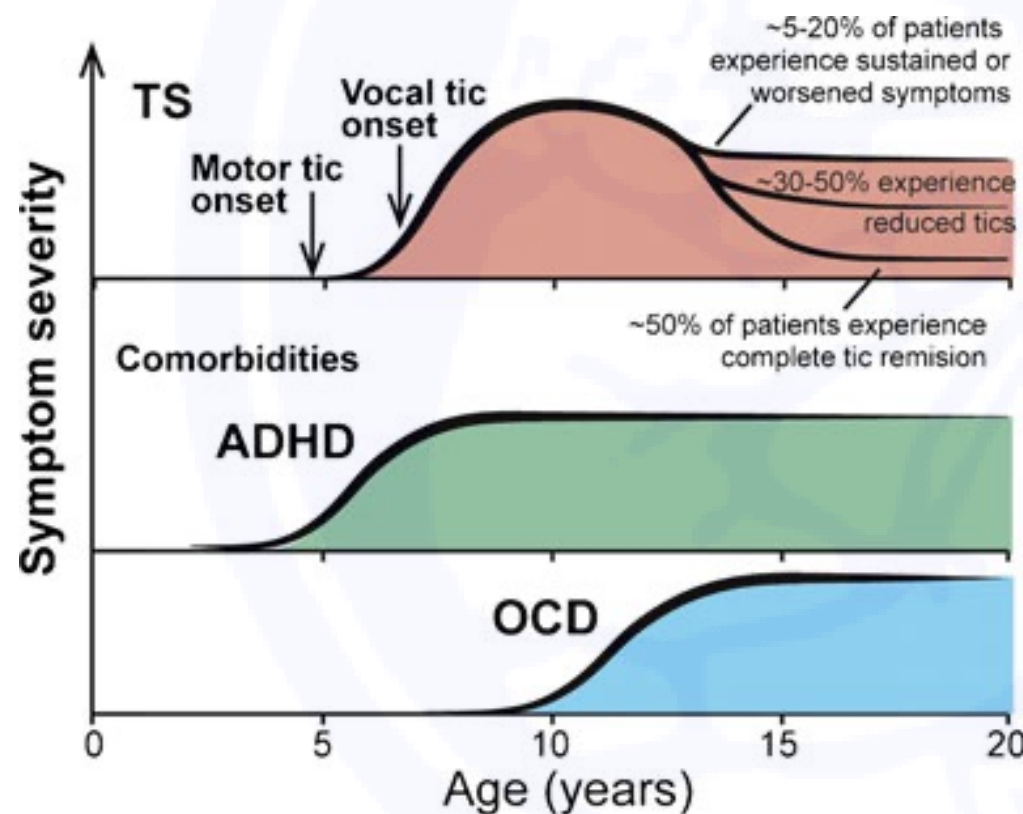
- Among children diagnosed with TS, 86% also have been diagnosed with at least one additional mental, behavioral, or developmental disorder
- 63% have **ADHD**
- 49% have **anxiety**
- More than one-third of people with TS also have **obsessive-compulsive disorder**.

## TOURETTE SYNDROME

Tics are just the tip of the iceberg



# Natural course of the disease



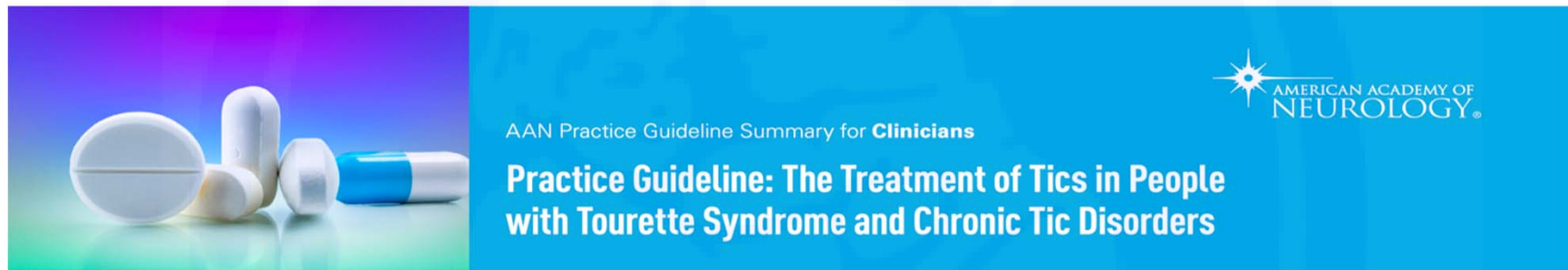
- ADHD ~ 3 years of age
- Motor tics (rostral-caudal progression) 5.6 years
- Vocal tics (simple -> complex)
- Tics peak ~11 years
- OCD can start 3 years later
- 60% of adolescents >16 yo have minimal or mild tics 6 years after the initial presentation

# When should we start treating?

Thorough medical history is crucial:

- Is the patient bothered by the tics?
- Do they cause pain or self-injury?
- Social distress?
- Interference with functioning in school or doing homework?
- Self-esteem?
- Risk of bullying?
- Are the comorbid conditions more problematic than tics?

# AAN Practice Guidelines

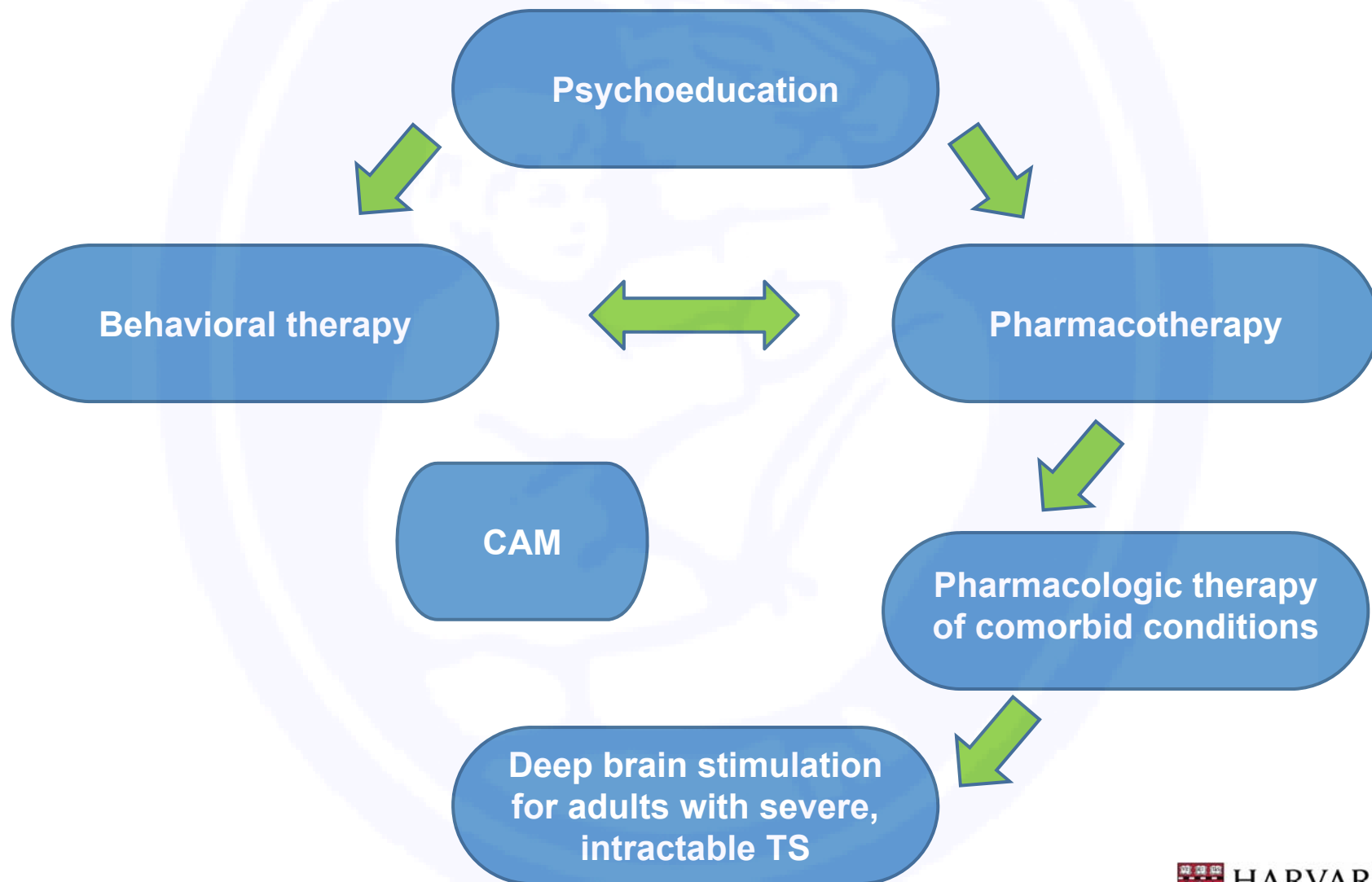


*Practice guideline recommendations summary: Treatment of tics in people with Tourette syndrome and chronic tic disorders*

Prigsheim et. al Neurology 2019

Endorsed by the Child Neurology Society and European Academy of Neurology

# Treatment options



# Pharmacologic treatment options

- Alpha-2 agonists
- Dopamine receptor blockers
- Dopamine depleters
- Topiramate
- Botulinum toxin
- Benzodiazepines
- GABA'ergic medications

# First line treatment options



“For people with tics who have access to CBIT, clinicians should offer CBIT as an initial treatment option relative to medication (Level B).”  
AAN Practice Guideline, 2019



# High confidence in the evidence

- AAN Practice guideline suggested high confidence that the Comprehensive Behavioral Intervention for Tics was more likely than psychoeducation and supportive therapy to reduce tics (Pringsheim et al. , 2019)
- CBIT has demonstrated efficacy for youth aged 9–17 years with CTD or TS (Piacentini et al., JAMA 2010)
- It aims to facilitate control of tics by disturbing the pattern of premonitory urges and the sensation of relief that follows the execution of the tics.

# What is CBIT?

Comprehensive Behavioral Intervention for Tics (CBIT) is a non-medicated treatment that consists of three major components:

- Training the patient to be more aware of the urge to tic (called premonitory urge) and to realize when he or she actually has tics.
- Training patients to do competing behavior when they feel the urge to tic.
- Making changes to day-to-day activities in ways that can be helpful in reducing tics.

# Challenges of CBIT

- Lack of therapists
- Cost especially if a therapist does not accept insurance
- Requires co-operation of the patient
- Recommended for children older than 9

# Alpha 2- receptor agonists

Used for mild to moderate tics, comorbid ADHD

**AAN 2019 Guideline - Level B evidence**

- **Clonidine (Kapvay, Catapres)**
  - May help attentional problems and impulsivity
  - Available in liquid (compound) and patch form
  - Can help with difficulty falling asleep if given at night
  - Starting dose 0.05- 0.1 mg/day
  - Therapeutic 0.1-0.4 mg/day (AACAP [Murphy 2013]; Pringsheim 2012)
  - Can lower BP and should not be stopped abruptly
- **Guanfacine (Tenex, Intuniv)**
  - Less sedating
  - Starting dose 0.5 – 1 mg/day
  - Therapeutic dose 1-4 mg/day

# Second line treatment options

“Physicians may prescribe antipsychotics for the treatment of tics when the benefits of treatment outweigh the risk (Level C).”

## TYPICAL ANTIPSYCHOTICS

Dopamine receptor antagonists

- Haloperidol (Haldol) *FDA approved*
- Pimozide (Orap) *FDA approved*
- Fluphenazine (Prolixin)

## ATYPICAL ANTIPSYCHOTICS

Dopamine and serotonin receptor antagonists

- Risperidone (Risperdal)
- Aripiprazole (Abilify) *approved in children*
- Ziprasidone (Geodon)
- Olanzapine (Zyprexa)
- Clozapine (Clozaril)
- Quetiapine (Seroquel)

## ANTI-CONVULSANTS

- Topiramate

# Side effects of neuroleptics

- Sedation
- Weight gain
- Metabolic syndrome (elevated glucose, hyperlipidemia)
- Gynecomastia, galactorrhea, amenorrhea (elevated prolactin level)
- Hypotension
- Arrhythmia (prolonged QT interval)
- “obtain EKG and measure QTc interval before pimozide and ziprasidone initiation” (Level A recommendation)
- Extrapyrasidal symptoms (akathisia, acute dystonic reaction, neuroleptic malignant syndrome, tardive dyskinesia (very rare)
- Depression

# Neuroleptics

## ATYPICAL ANTIPSYCHOTICS

Dopamine and serotonin receptor antagonists

- Risperidone (Risperdal)  
0.25-4 mg/day
- Aripiprazole (Abilify)  
2 -20 mg/day
- Ziprasidone (Geodon)  
5-40 mg/day
- Olanzapine (Zyprexa)  
5-10 mg/day
- Quetiapine (Seroquel)  
50-300 mg/day

- Less tight binding to the D2 receptor
- Usually better adverse effects profile but often cause weight gain
- Lower risk of tarditive dyskinesia
- Metformin may be necessary to counteract the metabolic syndrome



# Topiramate (Topamax, Trokendi XR, Qudexy XR)

- Should be used when benefits outweigh the risk (Level B)
  - Generally well-tolerated at low doses (25–150 mg/day)
  - Typical doses in kids (1-9 mg/kg/day), up to 200 mg in adults
  - Counsel about side effects: cognitive and language problems, somnolence, weight loss, renal stones (Level A)
  - Good alternative for patients with chronic headaches and migraines and/or obesity
- 
- (Jankovic et al., J Neurol Neurosurg Psychiatry, 2010, Donegan et al, Epilepsia 2015, Dell'Orto et. Al British Journal of Clinical Pharmacology 2014, Kramer *Obesity Reviews: an Official Journal of the International Association for the Study of Obesity*, 2011)

# Third line treatment options

## BOTULINUM TOXIN INJECTIONS

- Approved for treatment of adolescents and adults with localized and bothersome simple motor tics
- Side effects: weakness and hypophonia
- Needs to repeated every 12-16 weeks

## DOPAMINE DEPLETING AGENTS

- Tetrabenazine
- Deutetrabenazine
- Valbenazine

## DEEP BRAIN STIMULATION

- For patients with severe TS, resistant to medical and behavioral treatments

# Dopamine Depletors

## Tetrabenazine (Xenazine)

- Vesicular monoamine type 2 inhibitor (VMAT2)
- Presynaptic monoamine depletor, post-synaptic DA antagonist
- Only approved for Huntington's disease in the U.S.A
- Evidence in open label studies and retrospective reporting 77-80% of patients responding
- Typical dose 25-150 mg/day
- Associated with dose-related side effects such as drowsiness, depression, parkinsonism, weight loss and restlessness

(Kenney et al, J Pediatr Neurol, 2007, Janovic, Nature Reviews Neurology, 2017)

# Summary of VMAT Trials

Name of study	Sponsor	Name of drug	Phase	Design	Outcome
T-Force Gold	Neurocrine	Valbenazine (Ingrezza)	2b	Dose optimization study	Failed to meet primary end-point
T-Force Platinum	Neurocrine	Valbenazine (Ingrezza)	2	Randomized withdrawal study	Stopped early for futility
ARTISTS1	Teva	Deutetrabenazine (Austedo)	2/3	Flexible dose, open label extension	Failed to meet primary end-point
ARTISTS2	Teva	Deutetrabenazine (Austedo)	3	Fixed-dose	Failed to meet primary end-point

# Deep brain stimulation

- DBS delivers electricity to the nerve cells in the abnormal circuit and restores them to a more “normal” status
- In TS abnormal firing in cortico-striato-thalamo-cortical (CSTC) circuit, which controls movement execution, habit formation, and reward
- No consensus on the optimal targets:
  - Centromedian thalamus-parafascicular (CM-Pf)
  - Posteroventral lobus pallidus interna (pvGPi)
  - Anteromedial globus pallidus internal (amGPi)

(Galvan et al, Front Neuroanat 2015, Jimenez-Shahed, J. Neurol Clin, 2020)

# What other treatments can help?

- An impact survey conducted by The Tourette Association of America found that 47% of adults and 44% of the parents of children with Tourette Syndrome do not feel their or their children's symptoms are adequately controlled by existing medications.

<https://tourette.org/research-medical/>

# Marijuana and Tourette Syndrome

- Anecdotal case reports suggest that smoking marijuana or THC-containing products in various forms can potentially:
  - Reduce premonitory urge
  - Reduce tics
  - Improve sleep
  - Improve concentration
  - Help relaxation
  - Reduce depression, ADHD, OCD, rage attacks



# Effects of cannabinoids

Euphoria  
Spontaneous laughter and excitement  
Quiet and reflective mood  
Feelings of well being

Depend on the ratio of CBD and THC  
Route of administration  
Drug-drug interactions

Paranoia  
Anxiety  
Fatigue  
Increased appetite

Fatigue  
Dry mouth  
Loss of memory  
Dizziness

Risk of structural and functional alteration of the developing brain

# Cannabis-based medications

- AAN practice guideline paper 2019  
“Cannabis-based medications should be avoided in children and adolescents, not only due to paucity of evidence but due to the association between cannabis exposure in adolescence and potentially harmful cognitive outcomes in adulthood”.
  
- “When regional legislation allows, cannabis-based medications can be used in otherwise treatment-resistant adults with clinically-relevant tics (Level C)”.

# Cannabis-based medicines in development for TS

## Ongoing studies:

Safety and Efficacy of Cannabis in TS NCT03247244 (Toronto, CA)	A double-blind, randomized, crossover pilot trial to compare the efficacy and safety of three vaporized medical cannabis products with different THC and CBD contents, as well as placebo, in adults
CANNAbidnoids in the Treatment of TICS (CANNA-TICS) NCT03087201	A Randomized Multi-centre Double-blind Placebo Controlled Trial to Demonstrate the Efficacy and Safety of Nabiximols* in the Treatment of Adults With Chronic Tic Disorders

\*Nabiximols cannabinoid is approved outside of the US for the spasticity associated with MS

# Complementary Alternative Medications or Therapies

- 5-Ling granule (1 Class I study, Zeng Y, J Child Psychology Psychiatry 2016)
- Ningdong granule (1 Class II study, Zhao, J Int Med Res, 2010)
- Magnesium
- Vitamin B6
- Omega 3 Fatty Acids
- Biofeedback
- Transcranial magnetic stimulation
- Oral orthotic



# Treatment of comorbid conditions

## Prioritize the biggest problem

- Often times the comorbidities cause more impairment than tics alone and need to be carefully assessed.
- Choose the most appropriate pharmacologic treatment:
  - Consider methylphenidate or atomoxetine for ADHD
  - Medications for OCD and anxiety can improve tics
    - SSRIs for anxiety fluoxetine, sertraline
    - SSRIs for OCD include also fluvoxamine (+CBT)
- Reassess periodically, dose and duration of treatment is important

# Research

- There is a big need for a clinical and translational research in tic disorders, OCD and Tourettic OCD
- The pathogenesis of TS is still unclear and very complex.
- There is a dysfunction in the cortico-striato-thalamo-cortical (CSTC) circuit, which controls movement execution, habit formation, and reward.
  - multiple gene that causes TS
  - environmental factors such as infections, perinatal influences and behavioral conditions.

# Thank you!

