Tics and Tourette Syndrome

Joseph Jankovic, MD

Professor of Neurology, Distinguished Chair in Movement Disorders, Director, Parkinson's Disease Center and Movement Disorders Clinic, Department of Neurology, Baylor College of Medicine, Houston, Texas

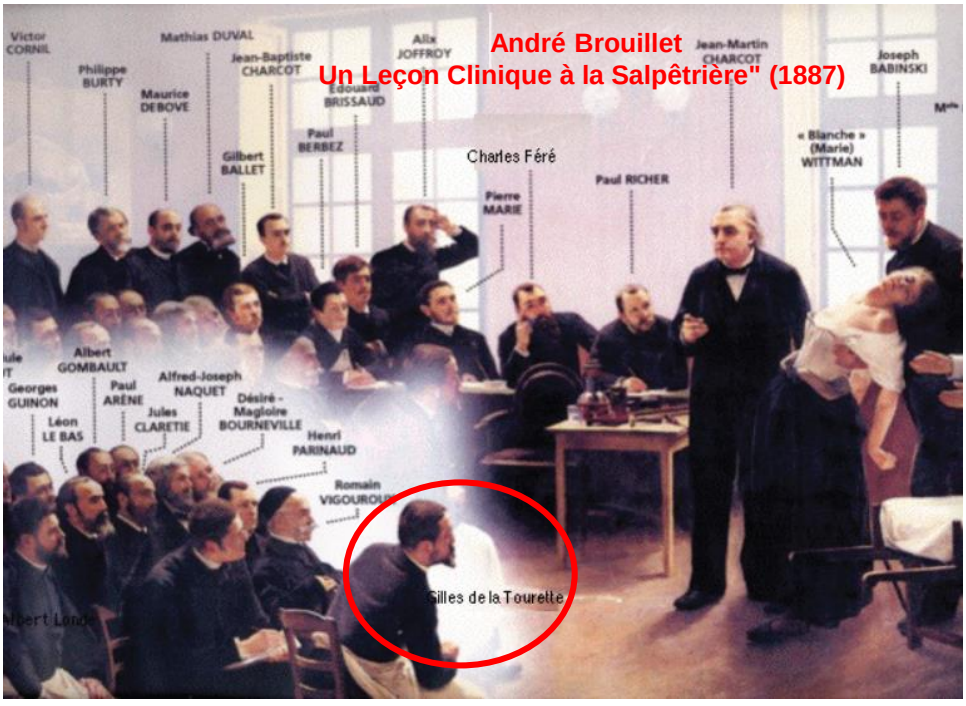
Gilles de la Tourette (1857–1904).

1885

9 patients

9 = motor tics
6 = phonic tics
5 = coprolalia
5 = echolalia
2 = echopraxia

Gilles de la Tourette G: Étude sur une affection nerveuse caracterisée par de l'incoordination motrice accompagnée d'echolalie et de copralalie. Arch Neurol (Paris)1885;9:158–200
("A study of a neurologic condition characterized by motor incoordination accompanied by echolalia and coprolalia")



Phenomenology ↔ Pathophysiology

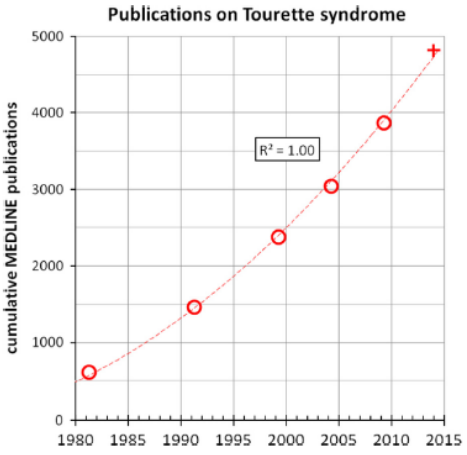
“To study the phenomenon of disease without books is to sail an uncharted sea, while to study books without patients is not to go to sea at all.”

Sir William Osler

William Osler. Aequanimitas. Books and Men. London: HK Lewis;1914:220

Progress in research on Tourette syndrome.

Black KJ, Jankovic J, Hershey T, McNaught KS, Mink JW, Walkup J.
J Obsessive Compuls Relat Disord 2014;3:359-362



Cumulative number of published articles on Tourette syndrome and other tic disorders.

Tics: Definition

- **Sudden, brief, intermittent, repetitive, non-rhythmic, involuntary or semi-voluntary movements or muscle contractions (motor tics) or sounds (phonic tics) which abruptly interrupt otherwise normal motor activity or speech.**

- **Motor tics**
  - **Simple or Complex**
    - **Clonic**
    - **Dystonic**
    - **Tonic (isometric)**
    - **Stereotypic**
    - **Blocking**
    - **Compulsive**
- **Phonic tics**
  - **Simple (meaningless sounds/noises)**
  - **Complex (semantically meaningful utterances)**
- **Sensory tics**
  - **Focal sensations (e.g. “tickle”, “itch”)**
  - **Premonitory sensation or urge (focal, generalized)**
  - **Sensory hypersensitivity**

"I already diagnosed myself on the Internet. I'm only here for a second opinion."

DSM-5 Diagnostic Criteria for Tourette's Disorder/Tourette Syndrome

- **A. Both multiple motor and one or more vocal tics are present at some time during the illness, although not necessarily concurrently.**
- **B. The tics may wax or wane in frequency but have persisted for more than 1 year since first tic onset.**
- **C. Onset is before age 18 years.**
- **D. The disturbance is not attributable to the physiological effects of a substance (e.g. cocaine) or a general medical condition (e.g. Huntington's disease, postviral encephalitis).**

***DSM-5* Code: 307.23**

ICD-10 Codes:

- **Tourette's disorder – F95.2**
  Also includes: Tourette syndrome and Gilles de la Tourette's disease or syndrome (motor-verbal tic)
- **Persistent (Chronic) Motor or Vocal Tic Disorder – F95.1**
  Single or multiple motor or vocal tics
- **Provisional Tic Disorder – F95.0**
  Tics present for less than 1 year
  (Replaced transient tics of childhood)
- **Tic disorder, unspecified – F95.9**

Sensory aspects of movement disorders

Neepa Patel, Joseph Jankovic, Mark Hallett

Lancet Neurol 2014; 13: 100–12

Parkinson's Disease Center and Movement Disorders Clinic, Department of Neurology, Baylor College of Medicine, Houston, TX, USA (N Patel MD, Prof J Jankovic MD); and Human Motor Control Section, NINDS, National Institutes of Health, Bethesda, MD, USA (Prof M Hallett MD)

Movement disorders, which include disorders such as Parkinson's disease, legs syndrome, and akathisia, have traditionally been considered to be disor predominantly from dysfunction of the basal ganglia. This notion has bee recognition of associated behavioural, psychiatric, autonomic, and other no of movement disorders include intrinsic sensory abnormalities and the underlying motor abnormality. The basal ganglia, cerebellum, thalamus, an sensory input, seem to play a key part in abnormal sensorimotor integrati phenomenology and physiological basis of sensory abnormalities, and about and related structures in somatosensory processing, and its effect on motor

Panel: **Sensory aspects of movement disorders**

Parkinson's disease
Pain, akathisia, olfactory loss, visual impairment, vestibular dysfunction, proprioceptive and kinaesthetic dysfunction, and sensory cueing

Dystonias
Pain, photosensitivity, alleviating manoeuvres, kinaesthetic dysfunction, abnormal temporal and spatial discrimination

Peripherally induced dystonia, tremor, other movement disorders, and complex regional pain syndrome
Pain, paraesthesias

Tics and Tourette's syndrome
Premonitory urge phenomena, enhanced sensory perception, alleviating manoeuvres

Restless legs syndrome
Urge phenomena, reduction of urge with bright lights

Akathisia
Urge phenomena, reduction with passive motion (perception of movement)

Stereotypies
Urge phenomena

Tardive pain
Painful mouth and vagina syndrome, and phantom dyskinesias

Leg stereotypy disorder
Urge phenomena

Paroxysmal kinesigenic and non-kinesigenic dyskinesias
Numbness, paraesthesias, crawling sensations in legs

Epileptic automatism
Self-stimulatory behaviour

Self-stimulatory behaviours associated with normal development, or metabolic, genetic, and autistic disorders, and other neurological disorders (Lesch-Nyhan, neuroacanthocytosis, etc)
Self-stimulatory (masturbatory) behaviour

Painful limb (painful legs and moving toes and painful arms and moving fingers)
Pain and discomfort presumably due to peripheral nerve damage

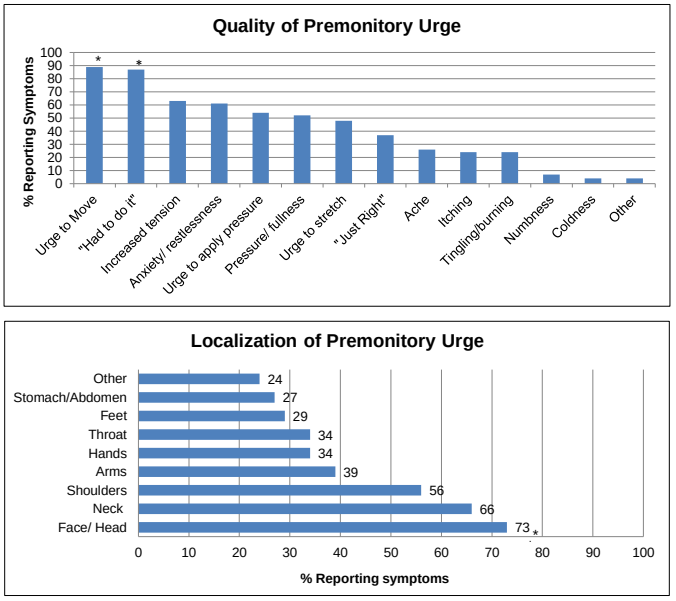
Huntington's disease
Abnormal nociception and visual perception

Tics: Characteristics

- **Premonitory feelings or sensations**
- **Regional or generalized sensory or mental phenomena or an urge that precede tics and are temporarily reduced by performance of tics**

PREMONITORY PHENOMENA

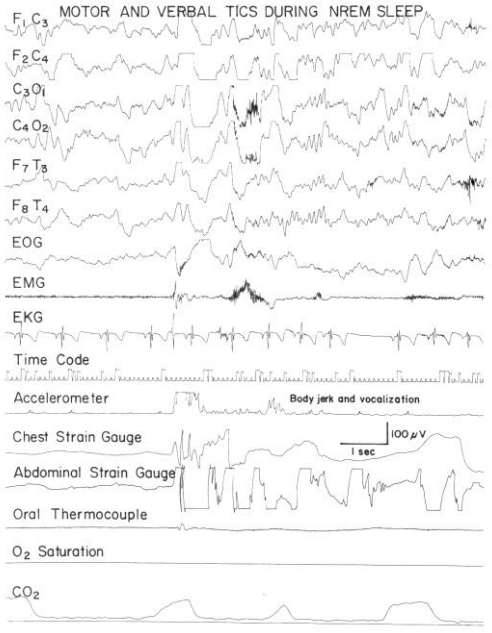
(reported by 92% of 50 patients)



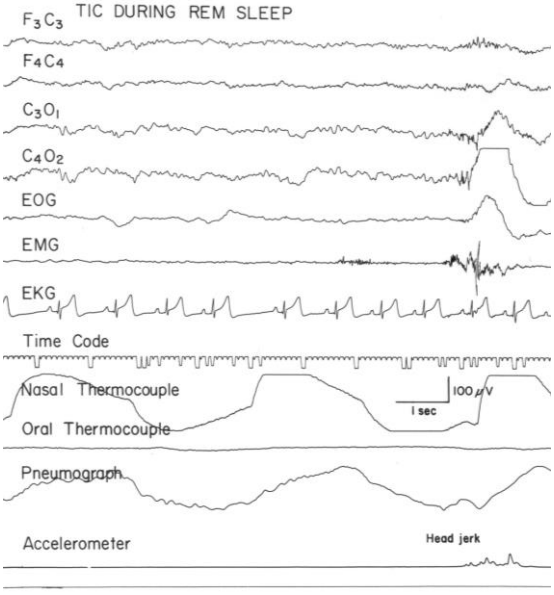
Kwak and Jankovic. Mov Disord 2003;18:1530-3

Tics: Characteristics

- Premonitory feelings or sensations
- **Brief and intermittent**
- **Repetitive (stereotypic)**
- **Temporarily suppressible**
- **Suggestible**
- **Increase/decrease with stress**
- **Increase during relaxation after stress**
- **Decrease with distraction and with concentration**
- **Change location, intensity, wax and wane, may remit for months or years**
- **Persist during sleep**



Glaze DG, Frost JD, Jankovic J. Neurology 1983;33:586-92



Glaze DG, Frost JD, Jankovic J. Neurology 1983;33:586-92

Polysomnography in TS

First Author/Yr	N	Age	REM	Arousal	Tics
Mendelson 1980	6	10-20	0	---	---
Glaze 1983	14	8-23	↓	↑	+
Jankovic 1987	34	<28	↓	↑	+
Drake 1982	7	10-36	↓	↑	---
Silvestri 1995	9	11-32	↓	↑	+
Voderholzer 1997	7	31±11	↓	↑	---
Rotheberg 2000	13	8-16	?	↑	+

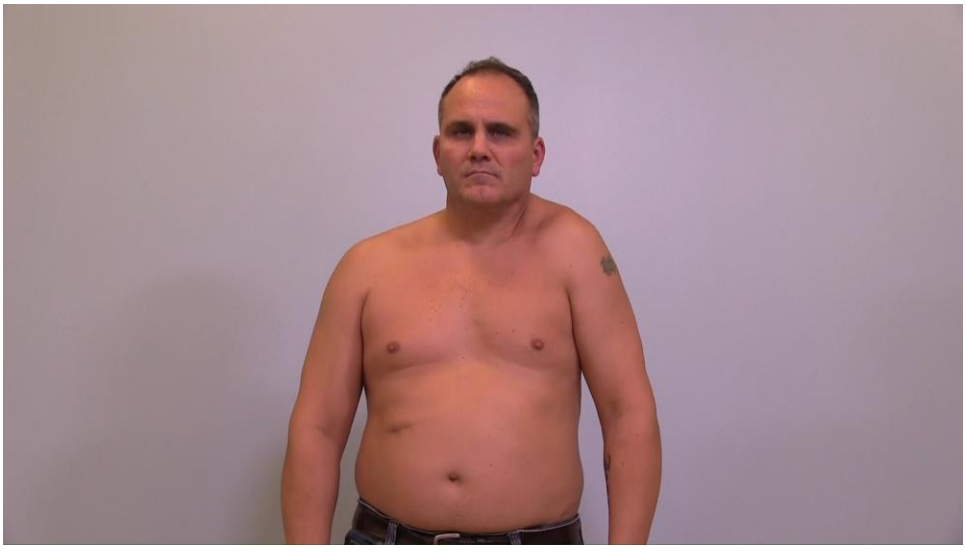
Hanna and Jankovic. Sleep and Movement Disorders 2003;464-71

Insomnia, excessive daytime sleepiness, disorders of arousal (sleepwalking, sleeptalking, sleep terrors, and enuresis), persistence of tics during sleep, and presence of periodic limb movements during sleep were very frequent in patients with TS, especially those with comorbid ADHD.

Jiménez-Jiménez et al. Sleep Med Rev 2020 (on line)

CERVICAL TICS

SHOULDER TICS



LIMB TICS

TRUNKAL-ABDOMINAL TICS

SIMPLE PHONIC TICS

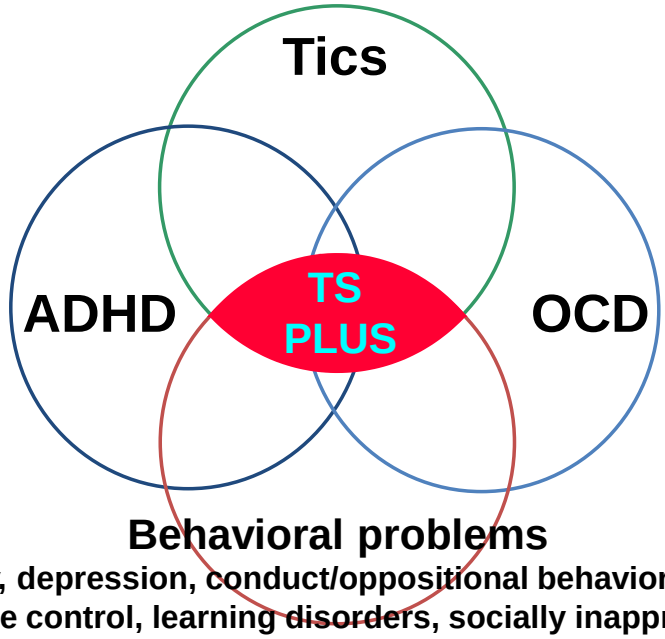
COMPLEX PHONIC TICS

14 y/o boy with stereotypic complex tics, anxiety and OCD

Complex tics released when examiner leaves the room

23 year old man with complex tics, OCD and anxiety

22 y/o with a 10-year hx of ADD, followed by simple and complex motor tics, blocking tics, shouting, coprolalia, and self-injurious behavior. The tics are usually preceded by a premonitory sensation and obsessive thoughts about performing the tics.



Behavioral problems

Anxiety, depression, conduct/oppositional behavior, loss of impulse control, learning disorders, socially inappropriate and self-injurious behaviors

Jankovic. Tourette's Syndrome. N Engl J Med 2001;345:1184-92

Tourette International Consortium

N (80 sites; 60% N. America; 66% Psychiatry; 27% Neurology)	6,805
Male:Female ratio	4.4 : 1
Mean age at onset of tics	6.4 years
Mean age at diagnosis of TS	13.2 years
Delay in diagnosis	6.4 years
Family history	51.7%
TS only, no comorbidity	14.2%
Attention Deficit/Hyperactivity Disorder	55.6%
Obsessive-Compulsive Disorder/Behavior	54.9%
Conduct/Oppositional Defiant Disorder	12.3%
Anger Control Problems	27.6%
Learning Disability	22.0%
Mood Disorder	16.9%
Anxiety Disorder	16.8%
Pervasive Developmental Disorder	4.6%

Freeman et al. Europ Child Adolesc Psychiatry 2007;16 (Suppl1):15-23

Lifetime Prevalence, Age of Risk, and Genetic Relationships of Comorbid Psychiatric Disorders in Tourette Syndrome.

Hirschtritt et al. JAMA Psychiatry 2015;72:325-33

- **Cross-sectional structured diagnostic interviews in 1374 TS patients and 1142 in TS-unaffected family members.**
- **Lifetime prevalence of comorbid DSM-IV-TR disorders in 85.7%; 57.7% of the population had 2 or more psychiatric disorders.**
- **72.1% of the individuals met the criteria for OCD or ADHD.**
- **Other disorders, including mood, anxiety, and disruptive behavior, each occurred in approximately 30% of the participants.**
- **The age of greatest risk for the onset of most comorbid psychiatric disorders was between 4 and 10 years, with the exception of eating and substance use disorders, which began in adolescence.**

Association of Tourette Syndrome and Chronic Tic Disorders With Objective Indicators of Educational Attainment: A Population-Based Sibling Comparison Study.

Perez-Vigil et al. JAMA Neurol 2018;75:1098-1105

- **Of the 2,115, 554 individuals in the Swedish cohort, 3,590 had registered a diagnosis of Tourette syndrome or a chronic tic disorder in specialist care (78.6% were male; median age at first diagnosis 14.0 years).**
- **Help-seeking individuals with Tourette syndrome or chronic tic disorders seen in specialist settings experience substantial academic underachievement across all educational levels, spanning from compulsory school to university, even after accounting for multiple confounding factors and psychiatric comorbidities.**

Coprophenomenon in TS

Freeman et al. Devel Med Child Neurol 2009;51;218-27

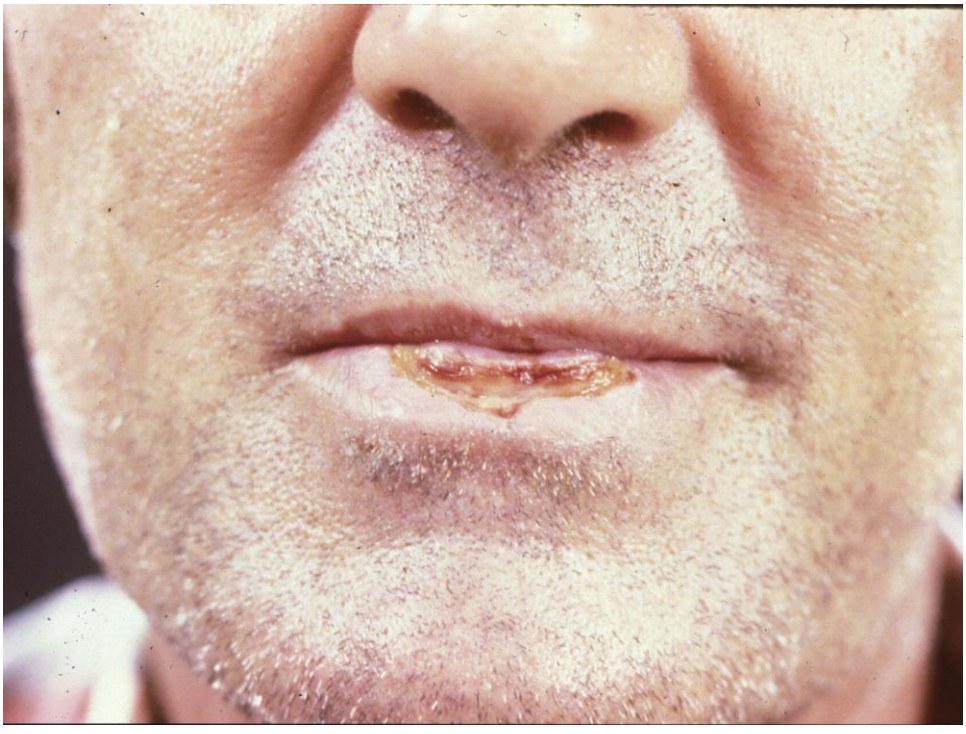
- **A specialized data collection form was completed for 558 consecutive new cases of TS, 15 sites, 7 countries**
- **Coprolalia occurred at some point in 19.3% of males and 14.6% of females; copropraxia in 5.9% of males and 4.9% of females**
- **Mean onset of coprolalia at 11 years and 10 years for copropraxia**
- **The mean onset of coprophenomena was 5 years after the onset of tics; in 11% of those with coprolalia this was the initial symptom of TS**

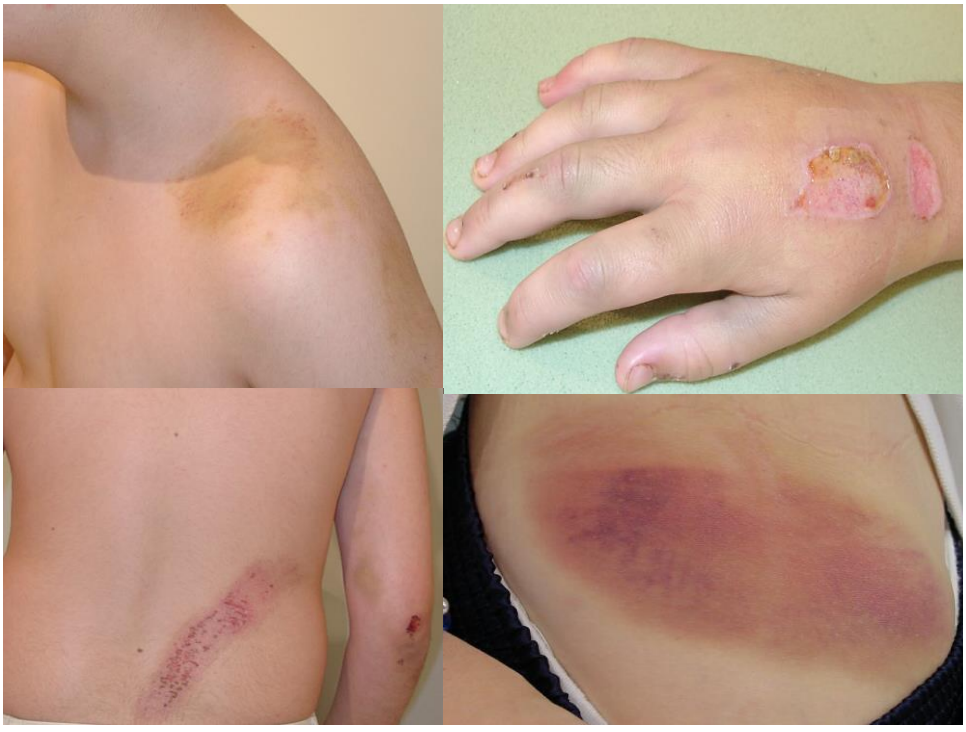
Coprolalia is usually in a form of uttering (swearing) obscenities (foul, repulsive, language often with sexual or scatological meaning), rather than profanity (cursing or cussing with religious meaning), although some have racist, sexist, or vulgar (coarse or crude) meaning

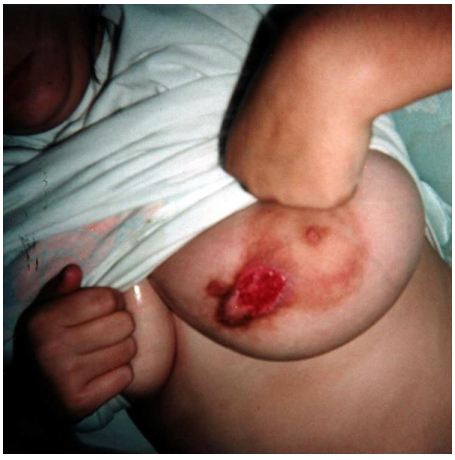
Malignant Tourette Syndrome

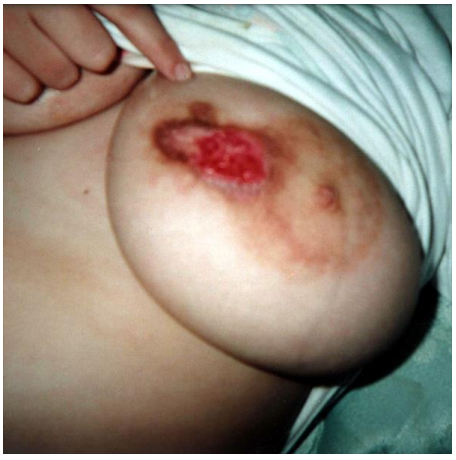
Cheung MC, Shahed J, Jankovic J. Mov Disord 2007;22:1743-50

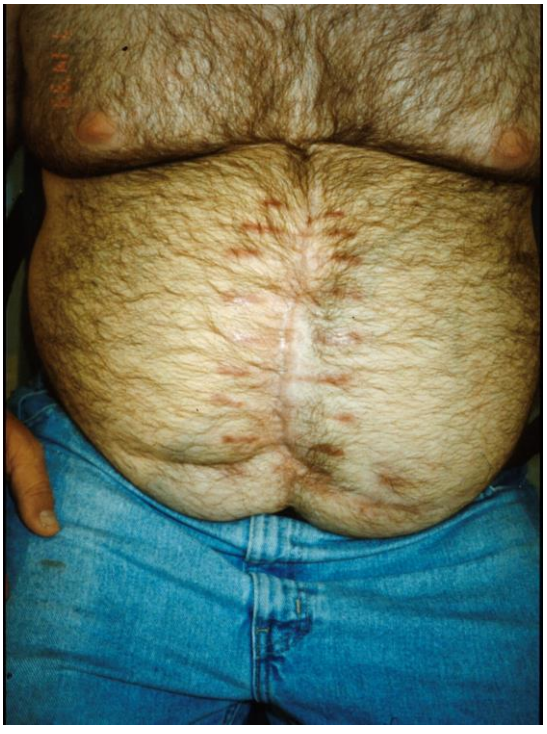
- **Malignant TS defined as ≥ 2 emergency room visits or ≥ 1 hospitalizations for TS symptoms or its associated behavioral co-morbidities**
- **Of 332 TS patients evaluated during the three-year period, 17 (5.1%) met criteria for malignant TS**
- **Compared to patients with non-malignant TS, those with malignant TS were significantly more likely to have a personal history of obsessive compulsive behavior/disorder, complex phonic tics, coprolalia, copropraxia, self-injurious behavior, mood disorder, suicidal ideation, and poor response to medications**







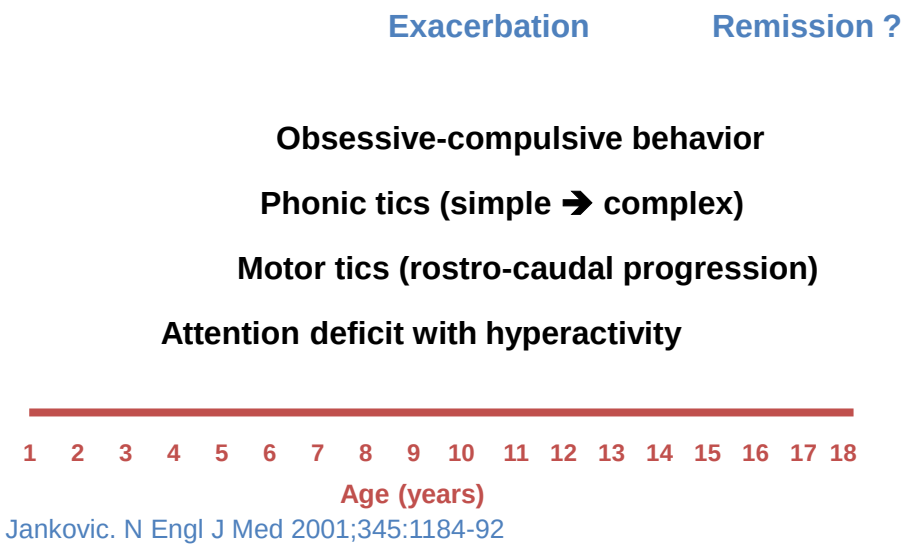




Malignant Tourette Syndrome

Throat swelling and difficulty breathing; hematemesis
Spinal cord compression; myelopathy with paraplegia, quadriparesis
Self-inflicted ear injury and abscess
Self-evisceration; self-inflicted gunshot wound; intestinal rupture
Self-stabbing in the neck with knives
Severe oral wounds from chewing inside of mouth requiring antibiotics
Hand lacerations requiring antibiotics and surgical debridement
Severe lip biting requiring re-attachment
Uncontrollable screaming and vocal cord blisters
Bilateral shoulder dislocations, hip dislocations, jaw injury
Uncontrollable aggression and violence, hallucinations, paranoia, verbal/physical violence
Self-inflicted thigh/abdominal wound requiring surgery; inserting objects into his wounds

Natural History of Tourette Syndrome

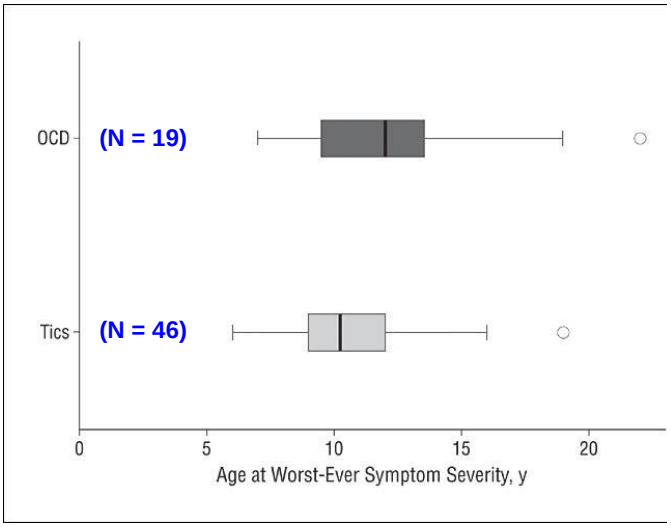


Jankovic. N Engl J Med 2001;345:1184-92

Age When Tic and OCD Symptoms Are at Their Worst

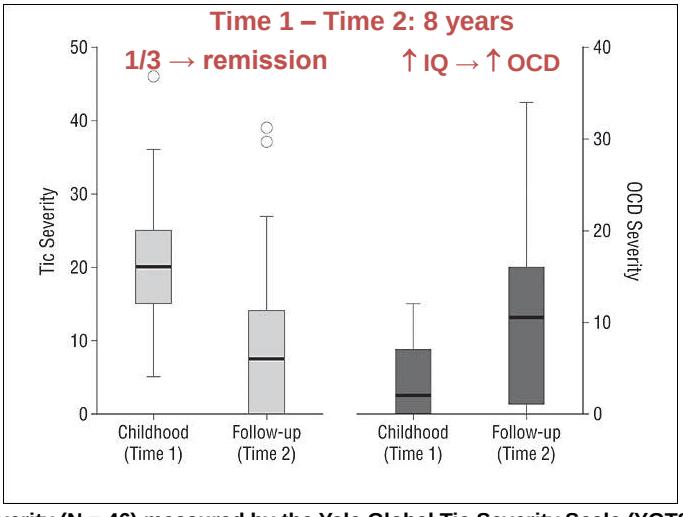
46 children with TS

Structured interview at a mean age of 11.4 years and again at 19.0 years



Bloch et al. Arch Pediatr Adolesc Med 2006;160:65-69

Tic and OCD Severity at Initial Assessment in Childhood (time 1) and Follow-up in Early Adulthood (time 2)



Tic Severity (N = 46) measured by the Yale Global Tic Severity Scale (YGTSS), OCD (N = 19) by the Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS)

Bloch et al. Arch Pediatr Adolesc Med 2006;160:65-69

Course of Tourette Syndrome and Comorbidities in a Large Prospective Clinical Study.

Groth et al. J Am Acad Child Adolesc Psychiatry 2017;56:304-12

- **The prospective clinical cohort was recruited at the Danish National Tourette Clinic and data were collected at baseline (n = 314, age range 5-19 years) and at follow-up 6 years later (n = 227).**
- **Tic severity declined yearly (0.8 points on the YGTSS) during adolescence; 17.7% of participants above age 16 years had no tics, whereas 59.5% had minimal or mild tics, and 22.8% had moderate or severe tics.**
- **At follow-up, 63.0% of participants had comorbidities or coexistent psychopathologies, whereas 37.0% had pure TS.**
- **Severity of tics, OCD, and ADHD were significantly associated with age and declined during adolescence, however, considerable comorbidities and coexisting psychopathologies persist throughout adolescence.**

Tourette Syndrome in Adults

Jankovic J, Gelineau-Kattner R, Davidson A. Mov Disord 2010;25:2171-5

- **We reviewed medical records of all new TS patients ≥19 y/o on initial evaluation referred to our Movement Disorders Clinic over the past 5 years and compared them with 100 TS patients ≤18 y/o**
- **The mean age of 43 adult TS patients was 58.8 ± 6.7 years**
- **Of the adult TS patients 35 (81.4%) had a history of tics with onset before age 18 (mean age at onset 8.5 ± 3.4 years); 8 (18.6%) reported first occurrence of tics after age 18 (mean age at onset 37.8 ± 13.2 years); only 2 (4.7%) patients reported tic onset after age 50**
- **Adult TS largely represents re-emergence or exacerbation of childhood-onset TS. During the course of TS, phonic and complex motor tics, self-injurious behaviors, and ADHD tend to improve, but facial, neck and trunk tics dominate the adult TS phenotype.**

Overall prevalence of TS in adulthood was estimated to be 118 cases of TS per million adults; male:female ratio: 2.33

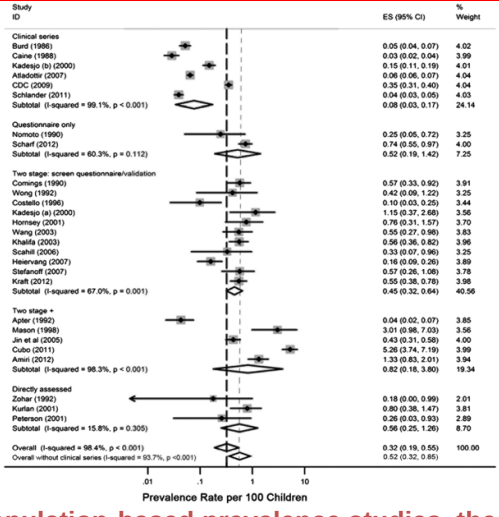
Levine et al. Prog Neuropsychopharmacol Biol Psychiatry 2019;95:109675

Epidemiology of TS

- **0.6% (3,034 children - Los Angeles)**
  Comings et al. J Clin Psychiatry 1990;51:463-9
- **0.7% (1,142 children, 2nd, 5th, 8th grades - Houston)**
  Hanna et al. Neurology 1999;53:813-8
- **6.1% (135/553 children; K - 6th grade - NIH) had TS; 24% observed to have motor tics during at least one month of the 8-month study**
  Snider et al. Pediatrics 2002;110:331-6
- **3.8% (339/1,596; 9 - 17y/o, - Rochester, NY) had TS; 21% had tics after 60-150 minutes of observation**
  Kurlan et al. Neurology 2002;59:414-20
- **Worldwide prevalence of TS in children: 0.3% to 0.8%**
  Scahill et al. Morb Mortal Wkly Rep 2009;58:581-5
- **0.3% of 13 y/o children had clinically definite TS and 0.7% had clinically probably TS based on a prospective study following 6,768 children in Avon, UK**
  Scharf et al. J Am Acad Child Adolesc Psychiatry 2012;51:192-201

Population prevalence of Tourette syndrome: a systematic review and meta-analysis.

Scharf et al. Mov Disord 2015;30:221-8



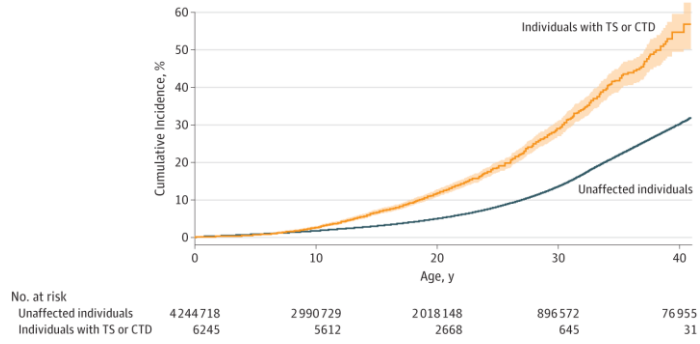
Among the 21 population-based prevalence studies, the pooled TS population prevalence estimate was 0.52%

(95% confidence interval CI: 0.32-0.85)

Association of Tourette Syndrome and Chronic Tic Disorder With Metabolic and Cardiovascular Disorders.

Brander et al. JAMA Neurol 2019;76:454-61

Cumulative Incidence of Any Cardiometabolic Disorder



Cumulative incidence for any metabolic or cardiovascular disorder among individuals with Tourette syndrome (TS) or chronic tic disorder (CTD) and unaffected individuals from the general population using the subgroup of individuals who were followed up from birth (N = 4,250,963).

Presumably not related to the use of antipsychotics.

What Causes Tourette Syndrome?

- **Brain autopsies – rare and not revealing**
- **Structural neuroimaging**
- **Functional neuroimaging**
  - **PET**
  - **FDG**
  - **Neurotransmitters**
  - **Functional MRI**
- **Neurophysiology**
- **Genetics**
- **Secondary tics**

Neuroimaging in Tourette Syndrome

MRI

- **Volumetric analyses of frontal and non-frontal areas show smaller gray matter of the left frontal lobe (loss of normal L > R asymmetry)**
  Fredericksen et al. Neurology 2002;58:85
- **Voxel-based morphometry and high-resolution MRI show increased gray matter in mesencephalon**
  Garraux et al. Ann Neurol 2006;59:381
- **Corpus callosum is smaller – compensatory reorganization (functional adaptation) as a result of enhanced motor control (suppression)?**
  Jackson et al. Curr Biol 2011;21:580

Study of medication-free children with Tourette syndrome do not show imaging abnormalities

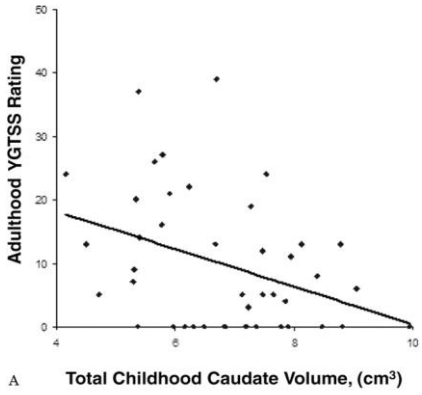
Jeppesen et al. Mov Disord 2014;29:1212-6

- **24 children with TS and 18 healthy controls were analyzed using three complementary MRI methods.**
- **Analyses revealed no differences between controls and patients with TS in gray or white matter.**
- **Possible discrepancies between cohorts and methods may play a role in the different findings in other studies.**

Neuroimaging in Tourette Syndrome

A prospective, longitudinal, study of 43 TS children, who had MRI before age 14 and again about 7.5 years later showed that caudate volumes correlate significantly and inversely with the severity of tics and OCD in early adulthood

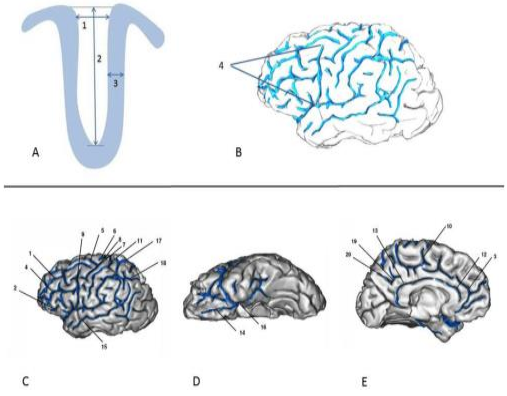
Bloch et al. Neurology 2005;65:1253



Altered structure of cortical sulci in Gilles de la Tourette syndrome: Further support for abnormal brain development.

Muellner et al. Mov Disord 2015;30:655-61

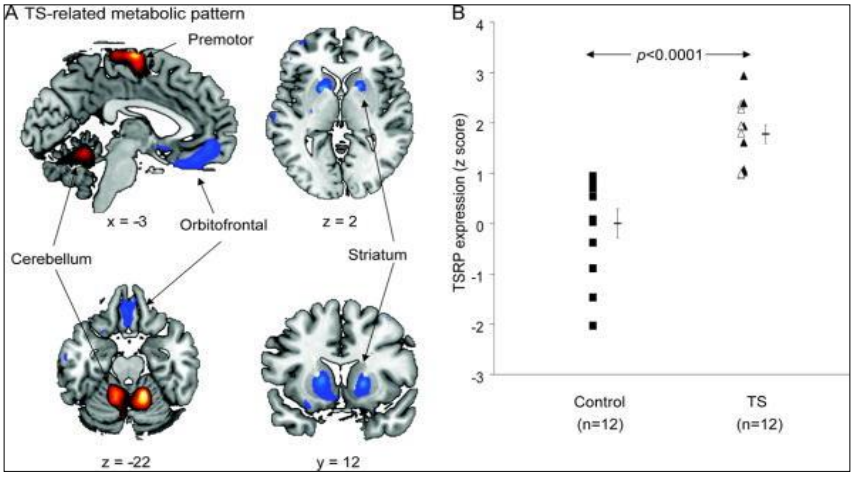
- **Using 3 Tesla structural neuroimaging, the investigators compared sulcal depth, opening, and length and thickness of sulcal gray matter in 52 adult patients with TS and 52 matched controls.**
- **Patients with TS had lower depth and reduced thickness of gray matter in the pre- and post-central as well as superior, inferior, and internal frontal sulci.**



Tourette syndrome-related pattern (TSRP)

Pourfar et al. Neurology 2011;76:944-52

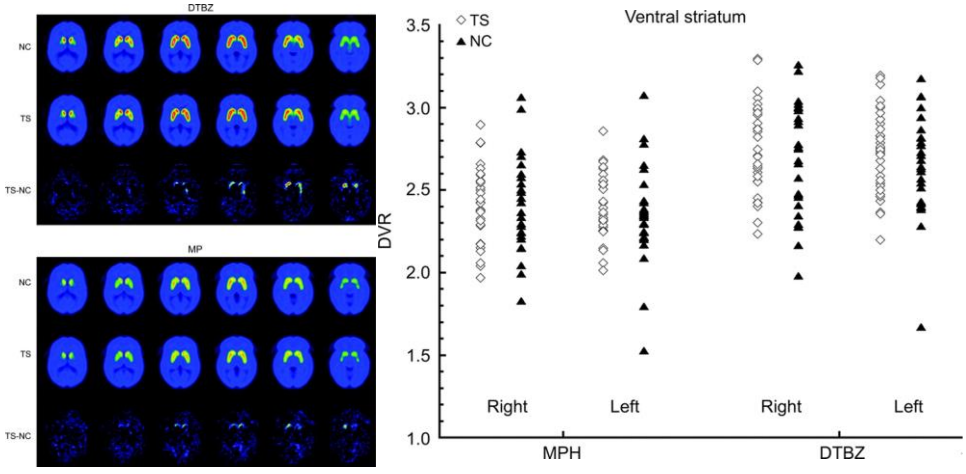
FDG PET scans (12 patients with adult TS and 12 healthy controls)
Metabolic increase in bilateral premotor cortices and cerebellum
covarying with metabolic decrease in caudate/putamen
and orbitofrontal cortices.



Striatal [11C]dihydrotetrabenazine and [11C]methylphenidate binding in Tourette syndrome.

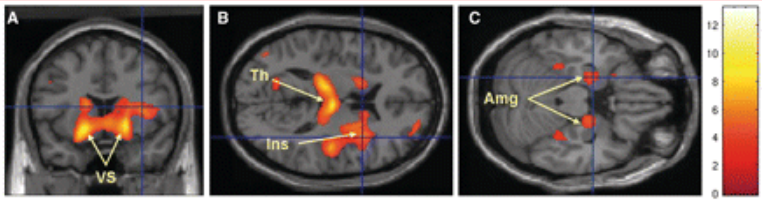
Albin et al. Neurology 2009;72:1390-6

No evidence of increased striatal dopaminergic innervation in TS

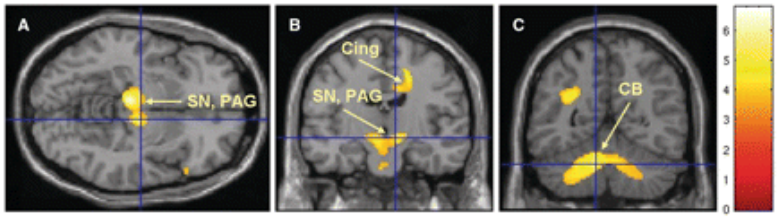


Widespread abnormality of the GABA-ergic system in Tourette syndrome.

Lerner et al. Brain 2012;135:1926-36



Decreased binding of [^{11}C]flumazenil: bilateral ventral striatum, bilateral thalamus, right insula and bilateral amygdala



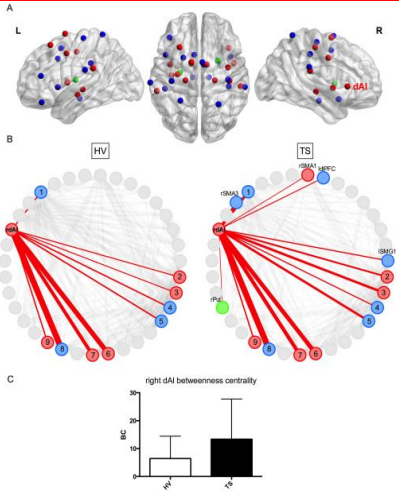
Increased binding of [^{11}C]flumazenil: bilateral substantia nigra, left periaqueductal grey, right posterior cingulate cortex and bilateral cerebellum, dentate nuclei

Primary defect in the GABA-ergic system → disinhibition

Role of the right dorsal anterior insula in the urge to tic in Tourette syndrome.

Tinaz et al. Mov Disord 2015;30:1190-7

- **Resting-state fMRI in 13 adult TS and 13 matched controls.**
- **The right dorsal anterior insula demonstrated higher connectivity, especially with the frontostriatal nodes of the urge-tic network and bilateral supplementary motor area.**
- **The right dorsal anterior insula also participates in urge suppression in healthy subjects.**
- **The right dorsal anterior insula may be part of the urge-tic network and could influence the urge- and tic-related cortico-striato-thalamic regions in TS.**



dAI = dorsal anterior insula

The role of the insula in the generation of motor tics and the experience of the premonitory urge-to-tic in Tourette syndrome.

Jackson et al. Cortex 2020;126:119-33

- **Using voxel-based morphometry techniques together with 'seed-to-voxel' structural covariance network mapping the putative role played by the right insular cortex in the generation of motor tics and premonitory urges were investigated in 39 patients with TS and 37 controls.**
- **Tic severity and premonitory urges are not always strongly associated with one another and may reflect largely independent phenomena.**
- **Motor tic severity scores were negatively associated with the grey matter volume values in a posterior region of the right insular while severity of premonitory urge was positively associated with grey matter volume values in a more anterior-dorsal region of the right insular cortex.**

Pathophysiology of Tics

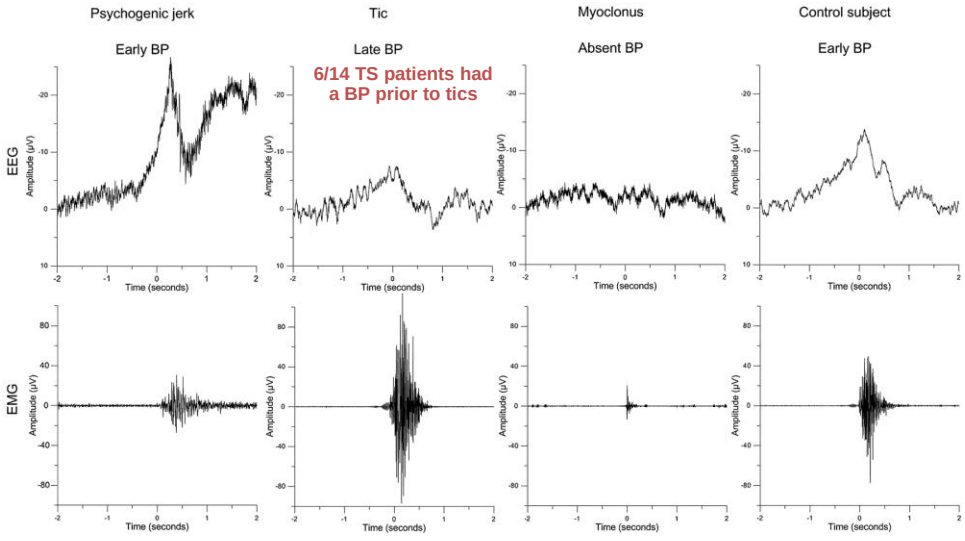
- **Transcranial Magnetic Stimulation: Shortened cortical silent period and reduced intracortical inhibition**

  Moll et al. Ann Neurol 2001;49:393-6; Orth et al. Biological Psychiatry 2008;64:248-51

- **Backaveraged EEG: Bereitschaftspotential absent prior to a tic in some, but not all patients**

The bereitschaftspotential in jerky movement disorders.

van der Salm et al. J Neurol Neurosurg Psychiatry 2012;83:1162-7

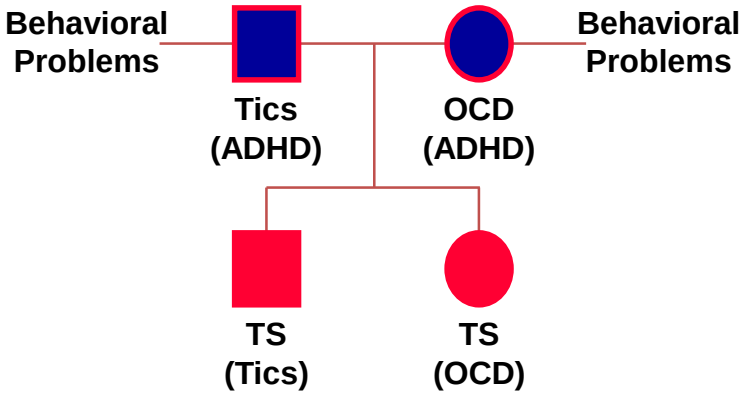


Differentiating tic electrophysiology from voluntary movement in the human thalamocortical circuit.

Cagle et al. J Neurol Neurosurg Psychiatry 2020;91:533-9

- **4 TS patients underwent monthly clinical visits for collection of physiology for a total of 6 months. Participants were implanted with bilateral CM thalamic macroelectrodes and M1 subdural electrodes that were connected to two neurostimulators, both with sensing capabilities.**
- **Recordings collected from the CM thalamic nucleus revealed an increase in a low-frequency (3-10 Hz) power that was time-locked to the onset of involuntary tics but was not present during voluntary movements. Cortical recordings revealed beta power decrease in M1 that was present during tics and voluntary movements.**
- **CONCLUSION: This physiological feature could potentially guide the development of neuromodulation therapies for TS that could use a closed-loop-based approach.**

Genetics of Tourette Syndrome



Bilineal Transmission

Assortative mating (like marry like)

Hanna et al. Neurology 1999;53:813-818

Heritability of Tourette Syndrome

- **Heritability estimate is 0.77 (95% CI, 0.70-0.85); there is a 15-fold increased risk in full siblings compared to that of the general population**
  Mataix-Cols et al. JAMA Psychiatry 2015;72:787-93
- **TS appears to be highly polygenic (genetic risk arises from a cumulative burden of hundreds of small effects size variants)**

Risk of developing TS

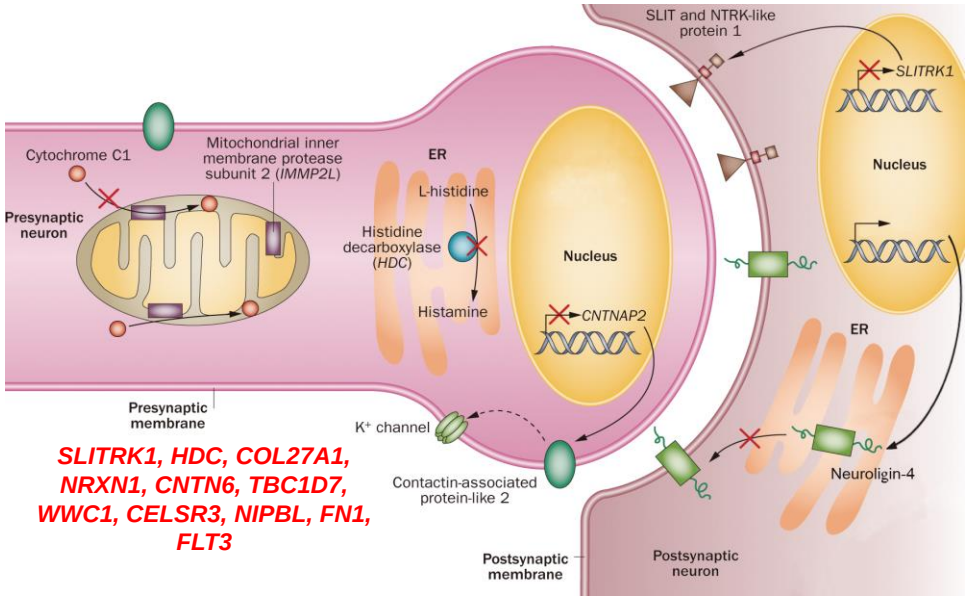
- **Nobody in the family has tics: 1-2%**
- **A family member has tics: 10-17%**
- **A non-identical twin has TS: 23%**
- **An identical twin has TS: 77%**

Interrogating the Genetic Determinants of Tourette's Syndrome and Other Tic Disorders Through Genome-Wide Association Studies.

Yu et al. Am J Psychiatry 2019;176:217-27

- **GWAS meta-analysis, gene-based association, and genetic enrichment analyses were conducted in 4,819 Tourette syndrome (TS) case subjects and 9,488 control subjects. Replication of top loci was conducted in an independent population-based sample (706 case subjects, 6,068 control subjects).**
- **GWAS and gene-based analyses identified one genome-wide significant locus within *FLT3* on chromosome 13, rs2504235, although this association was not replicated in the population-based sample.**
- **Genetic variants spanning evolutionarily conserved regions significantly explained 92.4% of TS heritability.**
- **TS-associated genes were significantly preferentially expressed in dorsolateral prefrontal cortex.**
- **Our genome-wide cell and tissue-based enrichment analyses implicate modulation of gene expression through noncoding variants as a fundamental mechanism in the pathogenesis of TS.**

Neuronal location and possible function of the gene products associated with Tourette syndrome



SLITRK1, HDC, COL27A1, NRXN1, CNTN6, TBC1D7, WWC1, CELSR3, NIPBL, FN1, FLT3

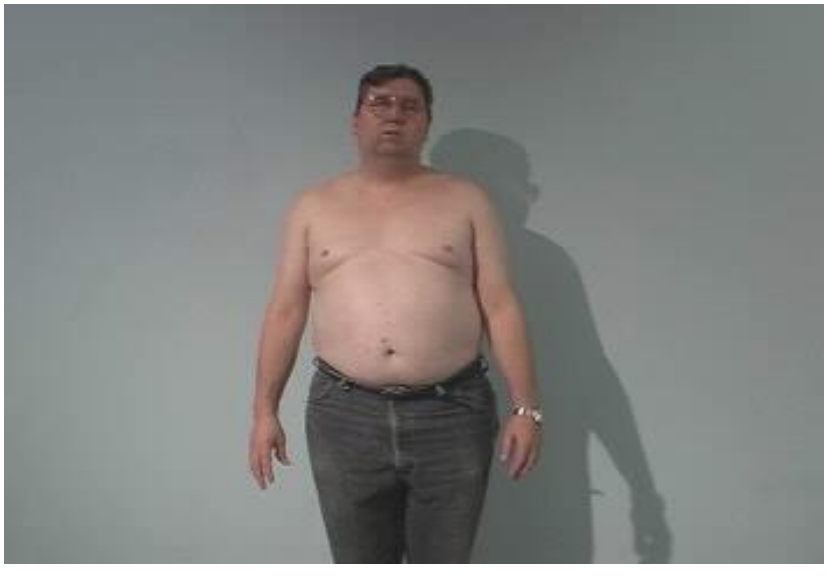
Deng H, Gao K, Le W, Jankovic J. Nature Reviews 2012;8:203-13

Secondary Tics

- **Genetic: HD, neuroacanthocytosis, autistic disorders, neurocutaneous syndromes**
- **Drugs: DRBD (antipsychotics, antiemetics), amphetamines, cocaine, levodopa, anticonvulsants**
- **Infectious/Immunologic: Encephalitis, C-J disease, Sydenham's chorea, PANDAS (?)**
- **Toxins: Carbon monoxide**
- **Other: Static encephalopathy, stroke, brain tumor, trauma (central and peripheral), psychogenic**

41 y/o – L shoulder motorcycle-related injury at age 22. Within 2 weeks developed L shoulder jerking, preceded by premonitory sensation and transiently suppressible. Has remained stable.

Erer S, Jankovic J. Parkinsonism and Rel Disord 2008;14:75-6



BE AWARE OF PANDAS!

P A N D A S

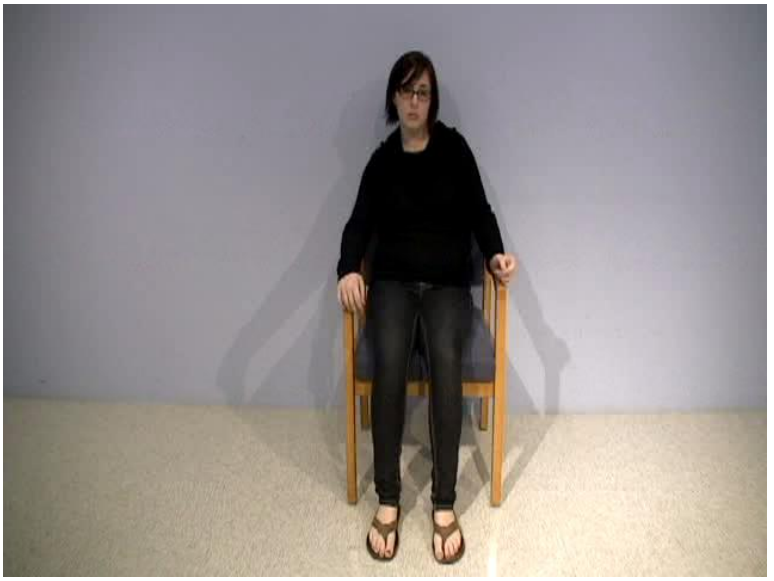
Pediatric
Autoimmune
Neuropsychiatric
Disorders
Associated with
Strep infections

P A N S

Pediatric
Acute-onset
Neuropsychiatric
Syndrome

Abrupt onset of OCD and acute neuro-psychiatric symptoms. In contrast to PANDAS, the diagnostic criteria for PANS no longer include tics.

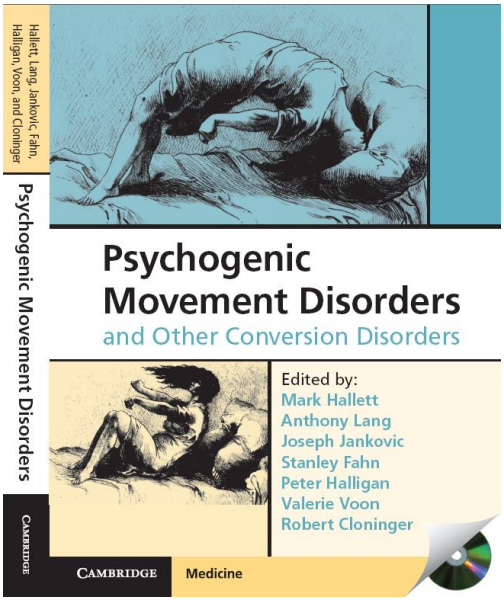
Xu et al. Antibodies From Children With PANDAS Bind Specifically to Striatal Cholinergic Interneurons and Alter Their Activity. Am J Psychiatry 2020 (online)

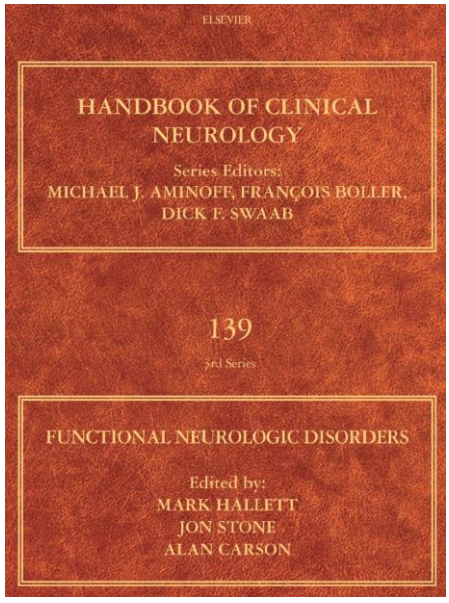


The Clinical Features of Psychogenic Movement Disorders resembling Tics and Stereotypies

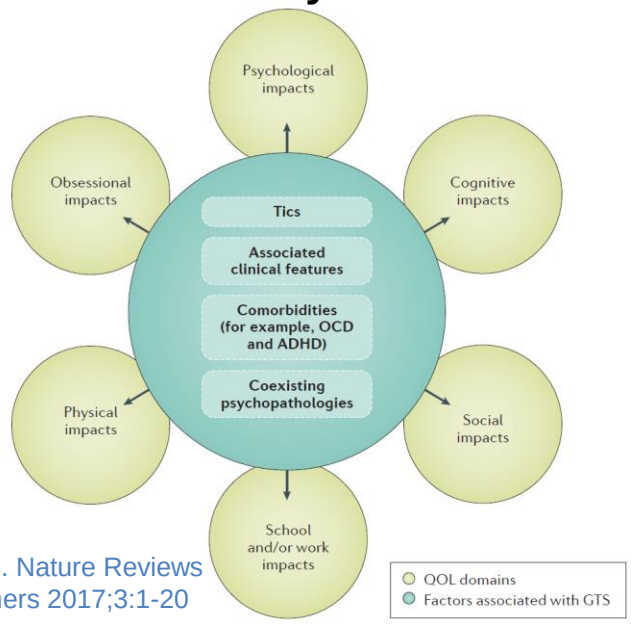
Baizabal-Carvallo JF, Jankovic J. JNNP 2014;85:573-5

- **9 patients, 5 females, with psychogenic tics diagnosed over a 3-year period.**
- **Mean age of onset: 29.7 years (range: 16-66).**
- **Psychogenic movement disorders resembling tics/stereotypies were observed in 4.9% of 184 patients first evaluated at BCM PDCMDC.**
- **Lack of premonitory sensations, incapable to (even) transiently suppress the movements, and frequent coexistence of other psychogenic movement disorders and pseudoseizures were common.**
- **Compared to 273 patients with Tourette syndrome, those with psychogenic tics were older: 36 vs. 18 years, (*P* = 0.014) at presentation and more frequently female: 55.6% vs. 21.5%, (*P* = 0.030).**
- **No patient with psychogenic tics reported childhood or family history of a tic disorder.**
- **Conclusions: Movements resembling tics/stereotypies can be observed in a small proportion of patients with psychogenic movement disorders. Clinical features can help to differentiate them from organic movement disorders.**





Quality of Life Domains Affected in Tourette Syndrome



Robertson et al. Nature Reviews Disease Primers 2017;3:1-20

Behavioral, Pharmacological, and Surgical Treatment of Tourette Syndrome

Clinical Assessments of Tourette Syndrome

- Yale Global Tic Severity Scale (YGTSS) – Total Tic Severity (TTS)
- TS-Clinical Global Impression (TS-CGI)
- TS-Patient Global Impression of Severity (TS-PGIS)
- TS-Patient Global Impression of Change (TS-PGIC)
- TS-Patient Global Impression of Impact (TS-PGII)
- Premonitory Urge for Tics Scale (PUTS)
- Tic-free interval
- Rush Video-based Tic Rating Scale (RVTRS)
- Mini International Neuropsychiatric Interview For Children and Adolescents (MINI–KID)
- Yale-Brown Obsessive-Compulsive Scale (Y-BOCS; CY-BOCS)
- Gilles de la Tourette Syndrome – Quality of Life Scale (GTS-QOL)
- Children's Depression Inventory 2 (CDI-2)
- Children's Columbia Suicide Severity Rating Scale (C-SSRS)

Treatment Options for Tourette Syndrome

Behavioral Therapy
- Comprehensive Behavioral Intervention for Tics (CBIT) and Habit Reversal Therapy (HRT)

Alpha agonists
- Clonidine
- Guanfacine

Dopamine Receptor Blockers
- Fluphenazine
- Risperidone
- Aripiprazole*
- Pimozide*
- Haloperidol*

Dopamine Depletors
- Tetrabenazine, Deutetrabenazine, Valbenazine

Antiepileptics
- Topiramate

Botulinum Toxin

Deep Brain Stimulation
- Thalamus
- Globus Pallidus Interna

* FDA approved

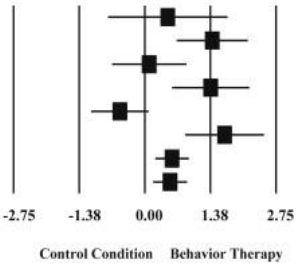
Thenganatt MA, Jankovic J. F1000Res 2016;9;5

A meta-analysis of behavior therapy for Tourette Syndrome

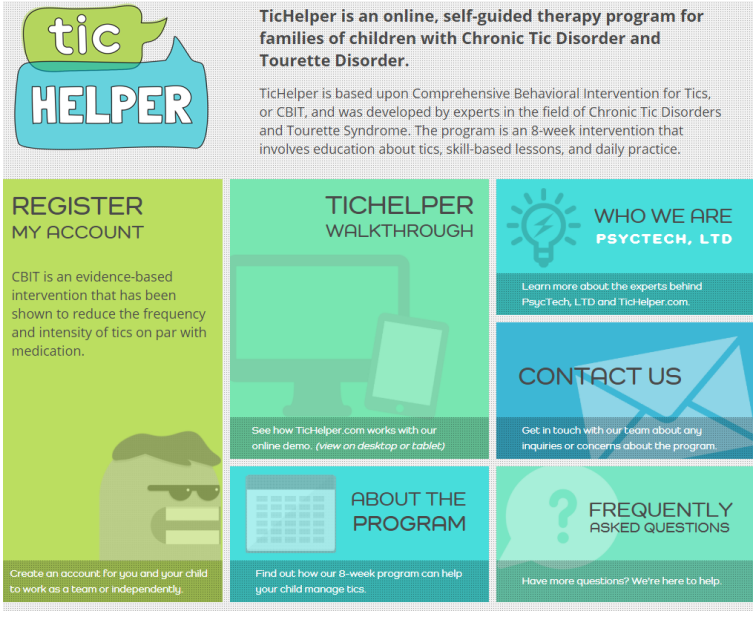
McGuire et al. J Psychiatr Res 2014;50:106-12

Randomized controlled trials (RCTs) of habit reversal training (HRT) and a Comprehensive Behavioral Intervention for Tics (CBIT) in TS. Overall, CBIT trials yield medium to large effects for TS that are comparable to treatment effects identified by meta-analyses of antipsychotic medication RCTs. Larger treatment effects may be observed among CBIT trials with older participants, more therapeutic contact, and less co-occurring ADHD.

Study name	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Azrin & Peterson, 1990	0.48	0.64	0.41	-0.78	1.74	0.75	0.453
O'Connor et al., 2001	1.41	0.38	0.15	0.66	2.16	3.70	0.000
Piacentini et al., 2002	0.09	0.40	0.16	-0.69	0.88	0.23	0.818
Wilhelm et al., 2003	1.38	0.42	0.17	0.57	2.20	3.33	0.001
Verdellen et al., 2004	-0.52	0.31	0.10	-1.13	0.09	-1.68	0.092
Deckersbach et al., 2006	1.67	0.42	0.18	0.84	2.50	3.94	0.000
Piacentini et al., 2010	0.57	0.18	0.03	0.22	0.93	3.15	0.002
Wilhelm et al., 2012	0.53	0.18	0.03	0.17	0.89	2.87	0.004



www.tichelper.com



Long-term efficacy and safety of fluphenazine in patients with Tourette syndrome

Wijemanne S, Wu LJC, Jankovic J. Mov Disord 2014;29:126-30

- **A retrospective chart review of patients with TS treated with fluphenazine over a 26-year period**
- **Response rating 1 through 5 (1 = marked reduction in tics, 5 = worsening of tics)**
- **N = 268 patients, 223 male and 45 female**
- **Mean age at start of fluphenazine was 15.8 ± 10.7 years (range 4.1-70.2) and it was the first line agent used in 187 (70%) patients**
- **Fluphenazine was continued for mean duration of 2.6 ± 3.2 years (range 0.01-16.8 years) and the mean daily dose at the end of treatment was 3.2 ± 2.3 mg per day (range: 0.5-12 mg)**
- **80.5% showed marked to moderate improvement (response rating 1 and 2) and none had worsening of symptoms**
- **51 (19.0%) patients discontinued fluphenazine due to side effects and 28 (10.4%) discontinued treatment due to lack of efficacy**
- **The most common adverse effects were drowsiness (26.1%), weight gain (11.6%), akathisia (8.5%), acute dystonic reaction (7.0%) and depression (6.3%). There were no cases of tardive dyskinesia.**

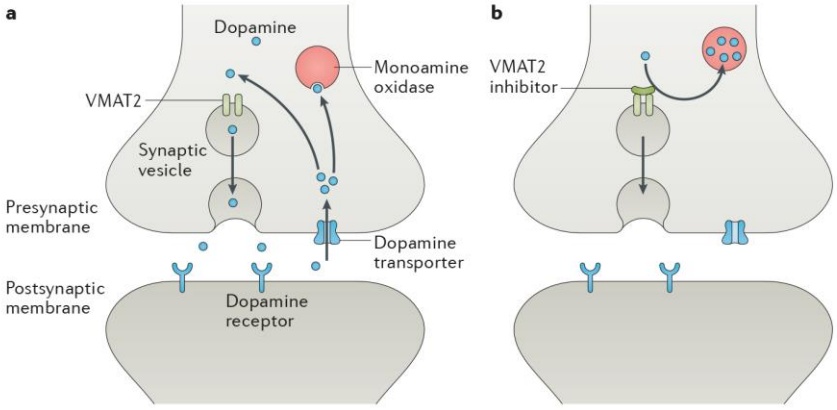
Randomized, Double-Blind, Placebo-Controlled Trial Demonstrates the Efficacy and Safety of Oral Aripiprazole for the Treatment of Tourette's Disorder in Children and Adolescents.

Sallee et al. J Child Adolesc Psychopharmacol 2017;27:771-781

- **Phase 3, randomized, double-blind, placebo-controlled trial which enrolled 133 patients.**
- **At week 8, the treatment difference in YGTSS-TTS vs placebo was -6.3 (p=0.0020) and -9.9 (<0.0001), respectively.**
- **Furthermore, 69% (29/42) of patients in the low-dose (5-10 mg/day) and 74% (26/35) of patients in the high-dose (10-20 mg/day) aripiprazole groups indicated that they were much or very much improved.**
- **The most common adverse events were sedation and fatigue.**

Peña MS, Yaltho TC, Jankovic J. Tardive dyskinesia and other movement disorders secondary to aripiprazole. Mov Disord 2011;26:147-52

Mechanism of action of VMAT2 inhibitors



Vesicular membrane transport type 2 (VMAT2) mediates loading of dopamine into synaptic vesicles for release. Breakdown of dopamine is mediated by monoamine oxidase.

VMAT2 inhibitors block transport of dopamine into synaptic vesicles, reducing dopamine release and depleting dopamine levels through its breakdown by monoamine oxidase.

VMAT2 inhibitors do not cause tardive dyskinesia

Jankovic. Nature Reviews Neurology 2017;13:76-78

Treatment Options for Tourette Syndrome

Behavioral Therapy
- Comprehensive Behavioral Intervention for Tics (CBIT) and Habit Reversal Therapy (HRT)

Alpha agonists
- Clonidine
- Guanfacine

Dopamine Receptor Blockers
- Fluphenazine
- Risperidone
- Aripiprazole*
- Pimozide*
- Haloperidol*

Dopamine Depletors
- Tetrabenazine, Deutetrabenazine, Valbenazine

Antiepileptics
- Topiramate

Botulinum Toxin

Deep Brain Stimulation
- Thalamus
- Globus Pallidus Interna

* FDA approved

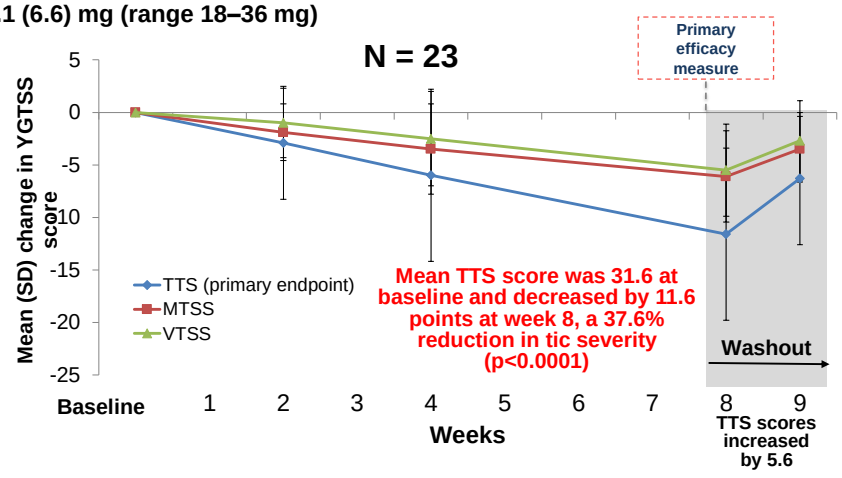
Thenganatt MA, Jankovic J. F1000Res. 2016;9;5

Before and after tetrabenazine

Deutetrabenazine in Tics associated with Tourette Syndrome.

Jankovic J, Jimenez-Shahed J, Budman C, Coffey B, Murphy T, Shprecher D, Stamler D. Tremor Other Hyperkinet Mov 2016;6:422

At Week 8, all three YGTSS measures were significantly reduced compared with baseline (P<0.0001) and the mean (SD) daily deutetrabenazine dose was 32.1 (6.6) mg (range 18–36 mg)



TTS = Total Tic Severity score

BDI and CY-BOCS also improved

Deutetrabenazine in Tics associated with Tourette Syndrome.

Jankovic J, Jimenez-Shahed J, Budman C, Coffey B, Murphy T, Shprecher D, Stamler D. Tremor Other Hyperkinet Mov 2016;6:422

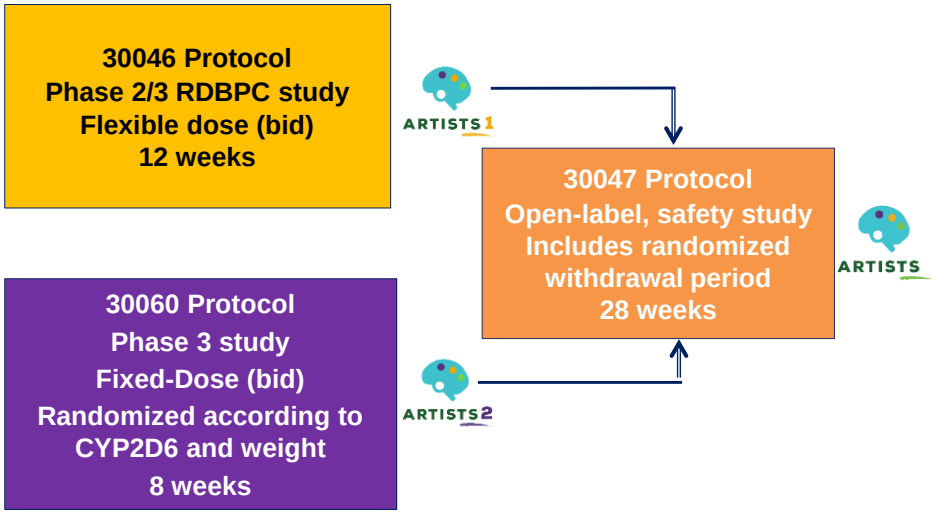
Safety Profile

	Deutetrabenazine N=23
Mean deutetrabenazine exposure, days (SD)	**54 (9.3)**
Mean daily dose at Week 8, mg (SD)	**32.1 (6.6)**
Patients with ≥1 AE, n (%)	**15 (65.2)**
AEs reported by ≥2 patients, n (%)	
Headache	**4 (17.4)**
Fatigue	**4 (17.4)**
Irritability	**3 (13.0)**
Nasopharyngitis	**2 (8.7)**
Somnolence	**2 (8.7)**
Hyperhidrosis	**2 (8.7)**
Diarrhea	**2 (8.7)**

- All adverse events were considered mild to moderate in severity
- One patient withdrew due to an adverse event (non-serious irritability unrelated to treatment) during the titration period
- **BDI-II assessment:** at Week 8, mean total score values decreased from baseline, indicating a reduction in depressive symptoms
- **C-SSRS assessment:** at Week 8, one patient reported suicidal ideation (mild), which was determined to be related to the patient's history of depression

Deutetrabenazine (TV50717) in Tourette Syndrome

Alternative in Reducing Tics in Tourette Syndrome (ARTISTS)

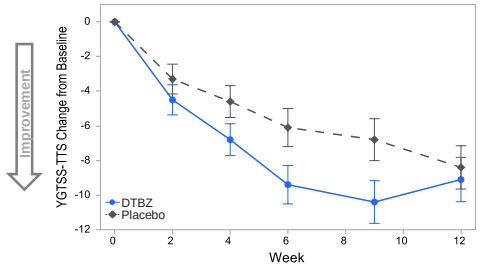


YGTSS Total Tic Severity (TTS) score ≥ 20

ARTISTS 1: TV50717-CNS-30046
Phase 2/3 flexible-dose study

119 participants, 6-16 y/o, were enrolled (DTBZ, N=59; placebo, N=60);
106 (89.1%) participants completed the study (DTBZ, N=50; placebo, N=56)

Although a favorable trend during titration was noted, the primary endpoint was not met



Primary Endpoint – YGTSS-TTS Change From Baseline to Week 12

Change from baseline to Week 12	DTBZ (N=58)	Placebo (N=59)
LS mean (±SE)	-9.1 (±1.28)	-8.4 (±1.25)
LS mean difference vs. placebo (95% CI)	-0.7 (-4.1, 2.8)	
Cohen's d	-0.073	
P value	0.692	

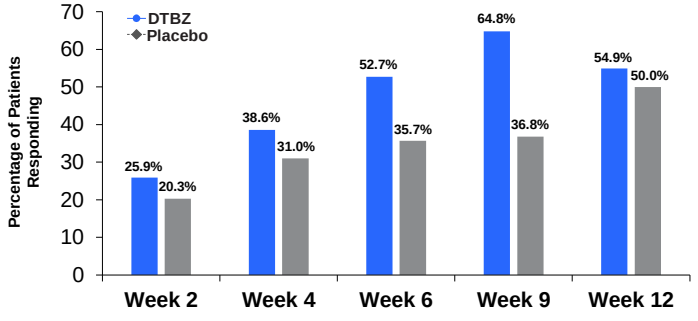
Secondary efficacy endpoint results were generally similar. There was no evidence of new safety signals, no evidence of depression or suicidal ideation.

DTBZ, deutetrabenazine; TTS, Total Tic Score; YGTSS, Yale Global Tic Severity Scale

ARTISTS 1: TV50717-CNS-30046
Phase 2/3 flexible-dose study

ARTISTS 1: Responder Rates at Each Visit by Treatment Group

Proportion of patients with ≥25% reduction from baseline in the TTS of the YGTSS

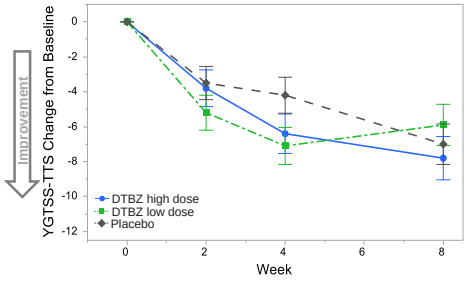


DTBZ, deutetrabenazine; TTS, Total Tic Score; YGTSS, Yale Global Tic Severity Scale

ARTISTS 2: TV50717-CNS-30060
Phase 3 fixed-dose study

158 participants were enrolled (DTBZ high dose, N=52; DTBZ low dose, N=54; placebo, N=52); of these, 145 (91.8%) participants completed the study (DTBZ high dose, N=46; DTBZ low dose, N=51; placebo, N=48)

Although a favorable trend during titration was noted, the primary endpoint was not met



Change from baseline to Week 8	DTBZ high dose (N=49)	DTBZ low dose (N=53)	Placebo (N=51)
LS mean (±SE)	-7.8 (±1.24)	-5.9 (±1.18)	-7.0 (±1.16)
LS mean difference vs. placebo (95% CI)	-0.8 (-3.9, 2.3)	1.1 (-1.9, 4.2)	
Cohen's d	-0.105	0.141	
P value	0.600	0.474[a]	

Primary Endpoint – YGTSS-TTS Change From Baseline to Week 8 (DTBZ high dose vs. placebo)

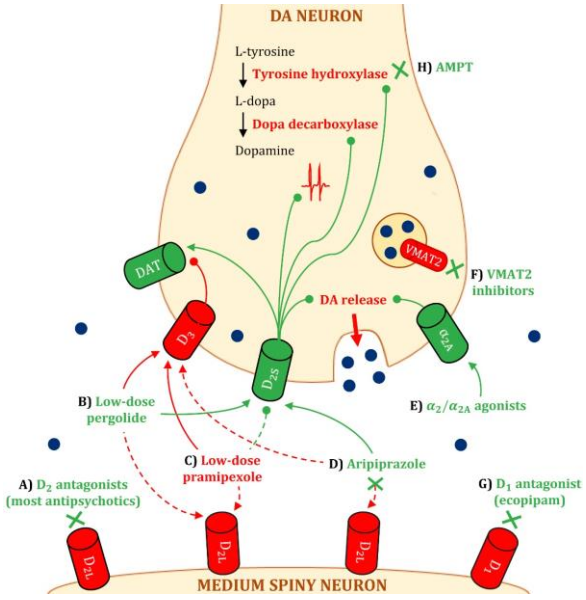
Secondary efficacy endpoint results were generally similar. There was no evidence of new safety signals, no evidence of depression or suicidal ideation.

DTBZ, deutetrabenazine; TTS, Total Tic Score; YGTSS, Yale Global Tic Severity Scale

Valbenazine (NBI-98854) in Tourette Syndrome

- **Phase 2 (T-Forward)**
  - **RDBPC study in 90 adults, age 18-64**
  - **8 weeks treatment, 2 fixed doses of valbenazine (qd)**
  - **While the study showed a significant improvement in overall symptoms of TS as evidenced by the Clinical Global Impression of Change (p=0.015), the pre-specified primary endpoint, the change-from-baseline in the Yale Global Tic Severity Scale (YGTSS) at week 8, was not met (p=0.18)**
- **Phase 2 (T-Force Green)**
  - **RDBPC study in 90 children, age 6-17**
  - **6 weeks treatment, 2 fixed doses of valbenazine (qd)**
  - **Failed to meet the primary endpoint**
- **Phase 3 (T-Force Gold)**
  - **RDBPC study in 180 children, age 6-17**
  - **Initial 6-week optimization phase followed by 6-week maintenance**
  - **Did not achieve its primary endpoint of a significant difference between placebo and active treatment groups in the change-from-baseline at week 12 on the YGTSS**
- **Phase 3 study (T-Force Platinum, in progress)**
  - **Randomized withdrawal**

Dopaminergic Pharmacology of Tourette Syndrome



Maia TV, Conceição VA. Biol Psychiatry 2018;84:332-44

Ecopipam, a D1 Receptor Antagonist, for Treatment of Tourette Syndrome in Children: A Randomized, Placebo-controlled Crossover Study

Donald L. Gilbert, MD,[1*] Tanya K. Murphy,[2] Joseph Jankovic, MD,[3] Cathy L. Budman, MD,[4] Kevin J. Black, MD,[5] Roger M. Kurlan, MD,[6] Keith A. Coffman, MD,[7] James T. McCracken, MD,[8] Jorge Juncos, MD,[9] Jon E. Grant, MD[10], and Richard E. Chipkin, PhD[11]

[1]*Cincinnati Children's Hospital Medical Center, Department of Pediatrics, Cincinnati, Ohio, USA*
[2]*University of South Florida, Departments of Pediatrics and Psychiatry, Tampa, Florida, USA*
[3]*Baylor College of Medicine, Department of Neurology, Houston, Texas, USA*
[4]*Zucker School of Medicine, Hofstra/Northwell Department of Psychiatry, Northwell Health, Hempstead, New York, USA*
[5]*Washington University School of Medicine, Departments of Psychiatry, Neurology, Radiology, and Neuroscience, St. Louis, Missouri, USA*
[6]*Center for Neurological and Neurodevelopmental Health, Voorhees, New Jersey, USA*
[7]*Children's Mercy Hospital, Kansas City, Missouri, USA*
[8]*UCLA Semel Institute for Neuroscience, Los Angeles, California, USA*
[9]*Emory University School of Medicine, Department of Neurology & Brain Health Center, Atlanta, Georgia, USA*
[10]*University of Chicago, Department of Psychiatry & Behavioral Neuroscience, Chicago, Illinois, USA*
[11]*Psyadon Pharmaceuticals, Inc., Germantown, Maryland, USA*

ABSTRACT: **Background**: Dopamine D2 receptor antagonists used to treat Tourette syndrome may have inadequate responses or intolerable side effects. We present results of a 4-week randomized, double-blind, placebo-controlled crossover study evaluating the safety, tolerability, and efficacy of the D1 receptor antagonist ecopipam in children and adolescents with Tourette syndrome. **Methods**: Forty youth aged 7 to 17 years with Tourette syndrome and a Yale Global Tic Severity Scale – total tic score of ≥20 were enrolled and randomized to either ecopipam (50 mg/day for weight of <34 kg, 100 mg/day for weight of >34 kg) or placebo for 30 days, followed by a 2-week washout and then crossed to the alternative treatment for 30 days. Stimulants and tic-suppressing medications were excluded. The primary outcome measure was the total tic score. Secondary outcomes included obsessive compulsive and attention deficit/hyperactivity disorder scales. **Results**: Relative to changes in placebo, reduction in total tic score was greater for ecopipam at 16 days (mean difference, -3.7; 95% CI, -6.5 to -0.9; $P = 0.011$) and 30 days (mean difference, -3.2; 95% CI, -6.1 to -0.3; $P = 0.033$). There were no weight gain, drug-induced dyskinesias, or changes in laboratory tests, electrocardiograms, vital signs, or comorbid symptoms. Dropout rate was 5% (2 of 40). Adverse events reported for both treatments were rated predominantly mild to moderate, with only 5 rated severe (2 for ecopipam and 3 for placebo). **Conclusions**: Ecopipam reduced tics and was well tolerated. This placebo-controlled study of ecopipam supports further clinical trials in children and adolescents with Tourette syndrome. © 2018 International Parkinson and Movement Disorder Society

Key Words: Tourette syndrome; ecopipam; dopamine D1 receptor; randomized; controlled trial; children

Mov Disord 2018;33:1272-80

Ecopipam, a D1 receptor antagonist, for treatment of Tourette syndrome in children: A randomized, placebo-controlled crossover study.

Gilbert et al. Mov Disord 2018;33:1272-80

- **Phase 2B study of 40 children ages 7-17 years meeting criteria for TS**
- **Reduction in total YGTSS (-12.4 vs -6.4) and YGTSS Total Tics scores (-5.6 vs -3.4) was greater for ecopipam treatment compared to placebo ($p < 0.05$).**
- **The percentage of patients showing much or very much improvement was 38% for ecopipam versus 18% for placebo ($p = 0.08$).**
- **Adverse events reported for both treatments (60 for ecopipam vs. 71 for placebo) were rated predominantly mild-to-moderate, with only 4 rated as "severe" and only one serious adverse event (unrelated).**
- **Conclusions: This is the first double-blind, placebo controlled study of ecopipam, a D1 receptor antagonist, in TS. Ecopipam appeared to be an efficacious and well-tolerated for TS in children and adolescents.**

Ecopipam, a D1 receptor antagonist, for treatment of Tourette syndrome in children: A randomized, placebo-controlled crossover study.

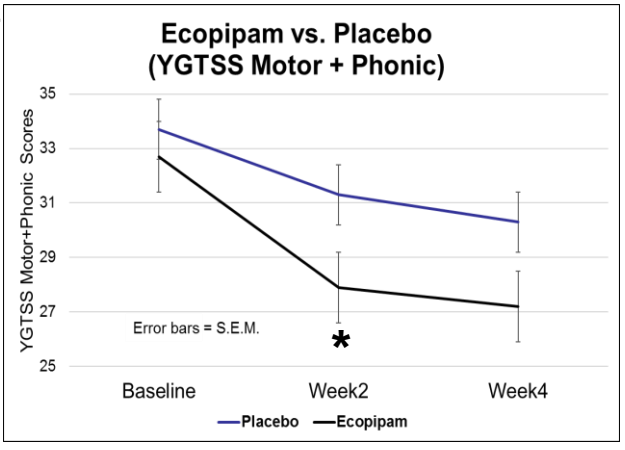
Gilbert et al. Mov Disord 2018;33:1272-80

N = 40, mean age 13.5±2.7

Total YGTSS decreased from 60.8 to 48.4 (-12.4) vs. from 61.2 to 54.8 (-6.4) p = 0.048

YGTS-TTS decreased from 32.8 to 27.2 (-5.6) vs. from 33.7 to 30.3 (-3.4) p = 0.043

Much or very much improved 38% vs 18% p = 0.08



*** YGTSS total tic scores were reduced vs. placebo at both 16 and 30 days (p≤0.05)**

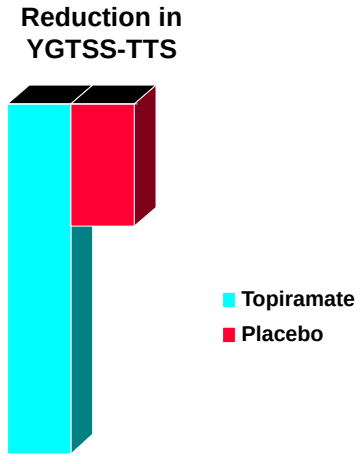
A Multicenter, Placebo-Controlled, Double-Blind, Randomized, Parallel-Group, Phase 2b Study to Evaluate the Efficacy and Safety of Ecopipam Tablets in Children and Adolescent Subjects with Tourette's Syndrome (D1AMOND)

- **Patients from 6 to 17 years old with a primary outcome of reduction in YGTSS (NCT04007991)**

A Randomized, Double-Blind, Placebo-Controlled Study of Topiramate in the Treatment of Tourette Syndrome

Jankovic et al. J Neurol Neurosug Psychiatry 2010;81:70-30

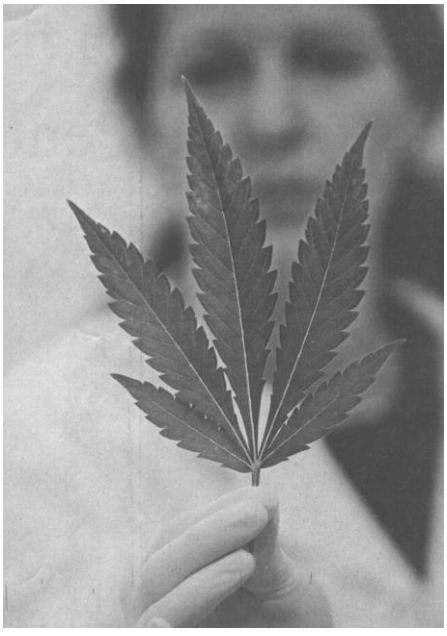
- **N = 29 (26 males)**
- **Mean age 16.5 ± 9.89 years**
- **The Total Tic Score (TTS), the primary endpoint, improved by 14.29 ± 10.47 points from baseline to visit 5 (Day 70) compared to 5.00 ± 9.88 point change in the placebo group (p = 0.0259)**
- **There were also improvements in the other components of the YGTSS and various secondary measures**
- **No differences were observed in the frequency of adverse events between the two treatment groups**



Topiramate (mean dose 118 mg)

Pimavanserin in Tourette Syndrome

- **Pimavanserin, a serotonin receptor inverse agonist, is FDA approved for treatment of psychosis in Parkinson's disease.**
- **In addition to dopaminergic dysfunction, imbalances in serotonergic, GABAergic, noradrenergic, glutamatergic, and cholinergic systems have been implicated in TS.**
- **Drugs that modulate serotonergic activity have been shown to be effective in treating tics and co-morbid OCD.**
- **An investigator-initiated, single center, open label, proof-of-principle, pilot study to evaluate the efficacy and safety over an 8-week period, in adults with TS.**
- **N= 20, TTS of YGTS ≥ 20, should be on a stable dose of anti-tic medications for 2 weeks.**
- **Pimavanserin 17 mg qhs for 1 week and, if the tics are deemed to be inadequately controlled then increased to 34 mg qhs, taken orally as two 17-mg tablets once daily.**
- **Primary Efficacy Measure: Reduction in TTS of the YGTSS after 8 weeks of treatment.**
- **Secondary measures: Y-BOCS, TS-CGI, TS-PGII, GTS-QoL, Tic-free interval, safety (including ECG).**



Netherlands has started to sell cannabis
September, 2003

"Legally grown cannabis: It will be used to relieve cancer, AIDS, multiple sclerosis and Tourette's"

Financial Times. Tuesday, September 2, 2003.

Treatment of Tourette syndrome with cannabinoids.

Müller-Vahl KR. Behav Neurol 2013;27:119-24

- **Several anecdotal reports provide evidence that marijuana might be effective not only in the suppression of tics, but also in the treatment of associated behavioral problems.**
- **Using both self and examiner rating scales, two controlled studies showed a significant tic reduction after treatment with THC compared to placebo, without causing significant adverse effects.**
- **"THC is recommended for the treatment of TS in adult patients, when first line treatments failed to improve the tics."**
- **According to a Cochrane review on the efficacy of cannabinoids in TS, definite conclusions cannot be drawn, because longer trials including a larger number of patients are missing.**
  Curtis et al. Cochrane Database Syst Rev 2009;(4):CD006565

REVIEW

The Therapeutic Potential of Cannabinoids for Movement Disorders

Benzi Kluger, MD, MS,[1†*] Piera Triolo, BS,[1†] Wallace Jones, BS,[1†] and Joseph Jankovic, MD[2†]

[1]*Movement Disorders Center, Department of Neurology, University of Colorado School of Medicine, Aurora, Colorado, USA*
[2]*Parkinson's Disease Center and Movement Disorders Clinic, Department of Neurology, Baylor College of Medicine, Houston, Texas, USA*

Mov Disord 2015;30:313-27

ABSTRACT: There is growing interest in the therapeutic potential of marijuana (cannabis) and cannabinoid-based chemicals within the medical community and, particularly, for neurological conditions. This interest is driven both by changes in the legal status of cannabis in many areas and increasing research into the roles of endocannabinoids within the central nervous system and their potential as symptomatic and/or neuroprotective therapies. We review basic science as well as preclinical and clinical studies on the therapeutic potential of cannabinoids specifically as it relates to movement disorders. The pharmacology of cannabis is complex, with over 60 neuroactive chemicals identified to date. The endocannabinoid system modulates neurotransmission involved in motor function, particularly within the basal ganglia. Preclinical research in animal models of several movement disorders have shown variable evidence for symptomatic benefits, but more consistently suggest potential neuroprotective effects in several animal models of Parkinson's (PD) and Huntington's disease (HD). Clinical observations and clinical trials of cannabinoid-based therapies suggests a possible benefit of cannabinoids for tics and probably no benefit for tremor in multiple sclerosis or dyskinesias or motor symptoms in PD. Data are insufficient to draw conclusions regarding HD, dystonia, or ataxia and nonexistent for myoclonus or RLS. Despite the widespread publicity about the medical benefits of cannabinoids, further preclinical and clinical research is needed to better characterize the pharmacological, physiological, and therapeutic effects of this class of drugs in movement disorders. © 2015 International Parkinson and Movement Disorder Society.

Key Words: cannabinoids; cannabis; movement disorders; Parkinson's disease; Huntington's disease

Other Experimental Drugs

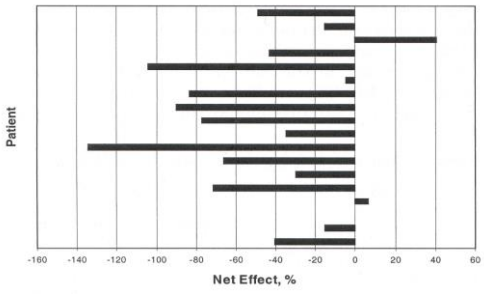
- **AZD5213**
  - Histamine H3 receptor antagonist
  - Phase 2 study completed
  - 0.5 mg vs 2mg vs placebo
  - 28 patients (12-17 y/o; TTS YGTS Score 22.9-25.4)
- **SNC-102**
  - Acamprosate calcium sustained release tablet
    - acts to restore balance between GABA and glutamate
  - Phase 2A open label trial
  - 8 week study: 800mg bid x 4 weeks, then 1600mg/800mg
  - 2/16 completed (ages 18-75)
- **ABX-1431**
  - Monoacylglycerol lipase inhibitor regulates 2-arachidonoylglycerol which signals through the cannabinoid receptors CB1 and CB2 to modulate neurotransmission
  - RDBPC crossover study in 19 adults with TS, patients receiving a single dose of ABX-1431 showed a 10% (placebo-adjusted, p= 0.0384) reduction in the Total Tic Score of the YGTSS

Botulinum Toxin for Motor Tics

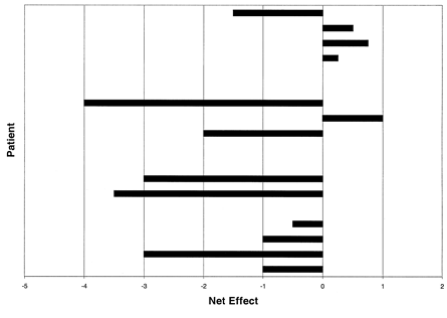
Marras et al. Neurology 2001;56:605-10

39% ↓ in tics/min with BTX vs 6% ↑ with placebo (*P* = 0.004)
0.46 ↓ in urge score with BTX vs 0.49 ↑ with placebo (*P* = 0.02)

Median Net Effect (at 2 weeks): –37% (p< 0.004)



tics/min



urge scores

Botulinum Toxin for the Treatment of Tics.

Lotia and Jankovic. Semin Neurol 2016;36:54-63

	Design	N	Injection Sites	Duration	Measures	Outcome	Comments
Kwak and Jankovic 2000	Open label case series	35	Upper and lower eyelid, eyebrow, paranasal muscles, masseters, SCM, submental complex, scalenus, trapezius, splenius, vocal cords	7 years at least one follow up or phone interview	Global response rating scale, peak effect scale, premonitory sensation.	29 patients with marked improvement. 78% improvement in global rating and 84% improvement in the premonitory sensation.	Subjective scale. Open label small study. Improvement in the urge sensation.
Marras et al 2001	RDBPC cross over	18	Blink, brow lift, head turn, neck extension, lower facial pull, shoulder shrug, neck flexion	2 weeks but followed over 12 weeks	Subjective urge scale, Shapiro Tourette syndrome scale tics/minute. Video recording.	39% improvement in the BoNT group and improvement in urge sensation. 50% reported weakness; although non-disabling it could have led to unblinding.	No change in severity score, tic suppression, pain, or PGI. Small sample size, mild symptoms, and a fixed treatment protocol.
Porta et al 2004	Open label case series. Phonic tics	22	2.5 IU of onabotulinumtoxinA in bilateral vocal cords	2 week phone call 2 follow up in a year	Hopkins vocal tic scale, Global impression, interference in life scale.	93% of patients with improvement in phonic tics with resolution in 50% improvement in frequency. Improved social life. 80% improvement in premonitory urge.	Open label single study. 80% had hypophonia.

Summary of Studies on Botulinum Toxin in Motor and Phonic Tics

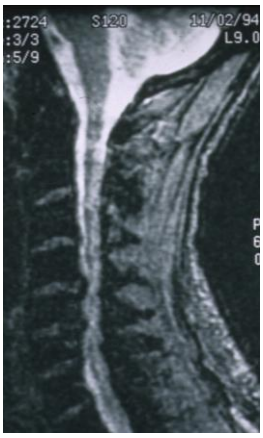
References	Type of Study	Type of Participants	Types of Intervention	Types of Outcome Measures	Conclusion
Jankovic[42]	Pilot study Open label	Cases: n = 10 (motor tics, all males)	BTX A	(1) Intensity and frequency of tics (2) PMUs	BTX injections (inj) appear to be safe and effective treatment for patients with focal dystonic tics. The treatment ameliorates not only involuntary movements but also the premonitory sensory component associated with some tics
Salloway et al[48]	Case report	One male (phonic)	BTX A	(1) Speech: loudness (UPDRS severity rating scale and 7-point scale) (2) Tic severity score and frequency (3) Premonitory tension	BTX led to a moderate reduction in the loudness of the tics, decrease in tic severity and frequency, may decrease the premonitory symptoms of tension and discomfort
Scott et al[49]	Case report	One male (phonic)	BTX A	Coprolalia and premonitory surge	BTX resulted in marked improvement in coprolalia as well as marked reduction in the premonitory urges associated with the vocal tics and coprolalia
Trimble et al[43]	Case report	One male (phonic)	BTX A	Coprolalia loudness intensity	Response to BTX was considerable, and affected not only the coprolalia, but also aided the general pattern of his symptoms, improved psychological state secondary to the relief of the coprolalia with its attendant psychosocial distress
Kwak et al[43]	Clinical trial	Cases: n = 35 (motor tics, 30 male, 5 female)	BTX A	(1) Clinical rating scale (0-4) (2) Patients' impressions of overall efficacy (3) Degree of benefit with premonitory sensations	BTX A improved the motor component of tics in all patients and also provided relief of premonitory sensations in 84% of the patients
Marras et al[41]	Randomized double-blinded controlled clinical trial	Cases: n = 18 (simple motor tics)	BTX	Primary: the number of treated tics per minute on a videotape segment Secondary: number of untreated tics per minute, the Shapiro Tourette Syndrome Severity Scale score, a numerical assessment of the urge to perform the treated tic and the patient's global impression of change	BTX reduced treated tic frequency (39% reduction; $P = 0.0007$) and the urge associated with the treated tic ($P = 0.02$). Despite these changes, patients did not report an overall benefit from the treatment
Porta et al[45]	Clinical trial Open label	Cases: n = 30 (only phonic tics)	BTX A	(1) Global impression of changes by physician and patient (2) PMU (3) Impact on quality of life	BTX A is an effective and safe treatment for phonic tics associated with Tourette syndrome (93% improved with 50% tic free, PMU dropped from 53% to 20%)
Srirompotong et al[47]	Case report	One male (ear wiggling tics)	BTX A	Disappearance of tics	There was complete disappearance of ear wiggling tics with BTX inj
Vincent[51]	Case series	Two cases with laryngeal tics (1 female, 1 male)	BTX A	(1) Clinical rating scale (2) Premonitory surge	Successful treatment with low-dose BTX type A to reduce the symptoms of laryngeal tics, premonitory surge leading to improved quality of life
Aguirregomozcorta et al[46]	Case report	One male (cervical dystonic tics)	BTX A	Resolution of cervical tics	Complete resolution of cervical dystonic tics with BTX in case of Tourette syndrome was seen
Rath et al[44]	Observational study	Cases: n = 30 (simple motor tics)	Not known	(1) Efficacy (rated on a 4-level scale) and duration of effect (2) Latency of response, changes of PMU and possible side effects	BTX A appears a safe and effective treatment for simple motor tics and retains its efficacy after long-term treatment. BTX may also induce permanent remission of the treated tics

Pandey S, Dash D. Neurologist 2019;24:93-108

Malignant Tourette Syndrome

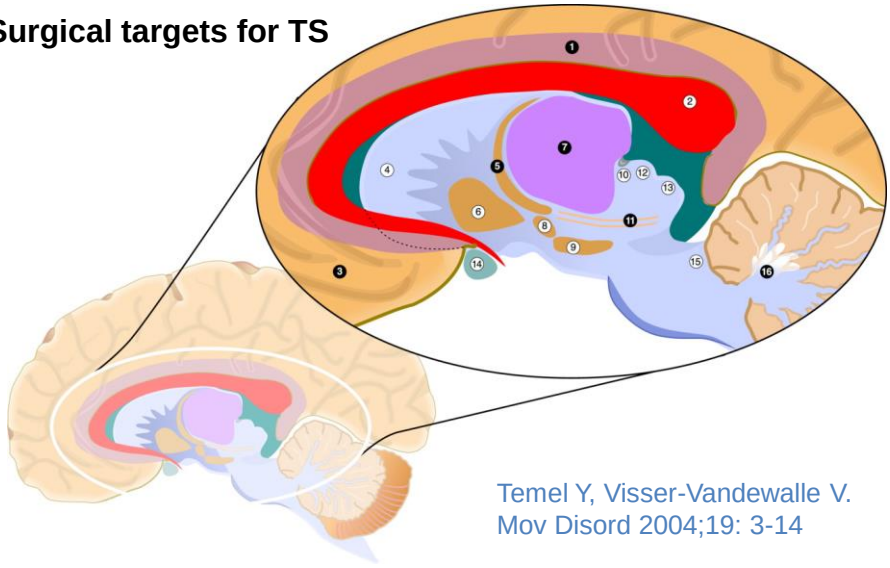
Cheung MC, Shahed J, Jankovic J. Mov Disord 2007;22:1743-50

"In one patient with a "whiplash" tic causing compressive cervical myelopathy, we were able to reverse the neurological deficit with botulinum toxin injections into the cervical muscles. This treatment modality can be particularly effective and even life-saving in patients with tics manifested by severe, repetitive, neck extension, the so called "whiplash tics". Such tics, if left untreated could results in secondary compressive myelopathy and quadraparesis."



Krauss JK, Jankovic J. Severe motor tics causing cervical myelopathy in Tourette's syndrome. Mov Disord 1996;11:563-6

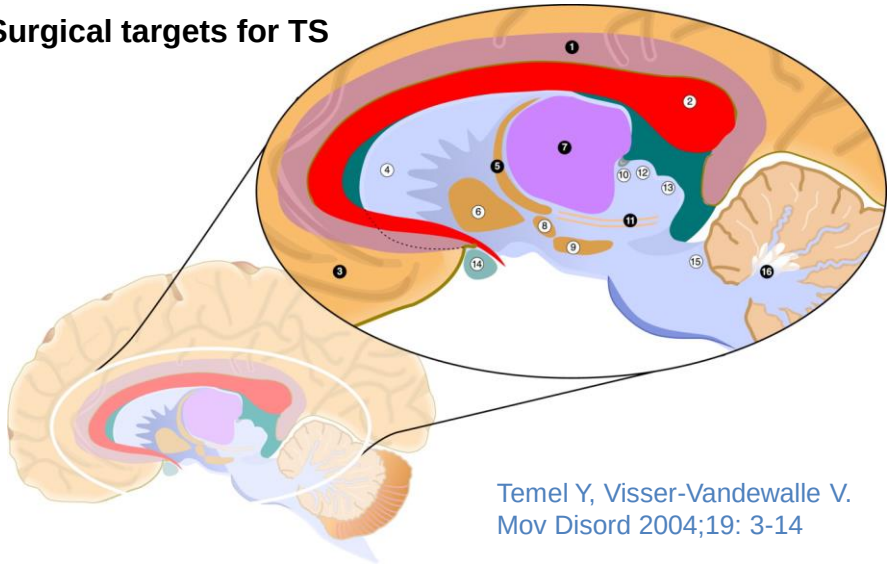
Surgical targets for TS



Temel Y, Visser-Vandewalle V. Mov Disord 2004;19: 3-14

1. cingulate cortex, 2. corpus callosum, 3. frontal lobe, 4. caudate-putamen, 5. zona incerta, 6. globus pallidus, 7. thalamus, 8. subthalamic nu, 9. substantia nigra, 10. posterior commissure, 11. H fields of Forel, 12. superior colliculus,13. inferior colliculus, 14. optic chiasm, 15. superior cerebellar peduncle, 16. dentate nucleus

Surgical targets for TS



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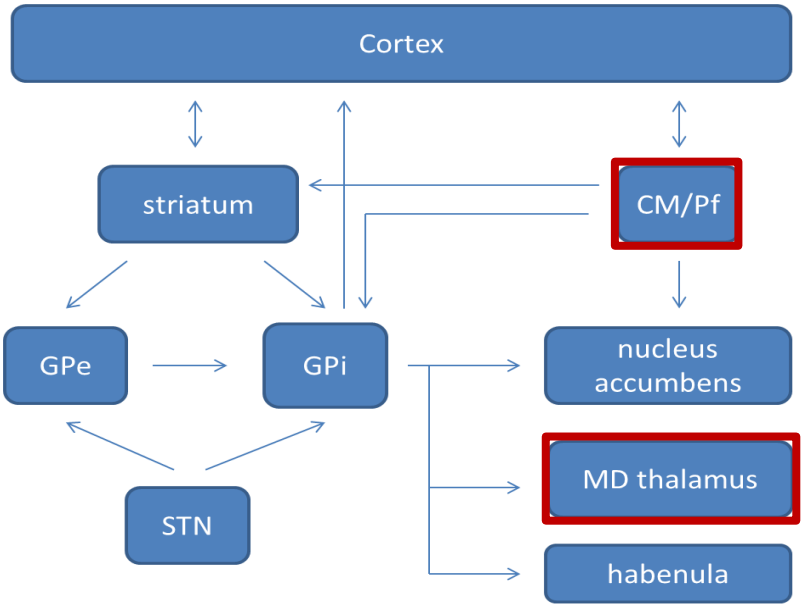
Deep Brain Stimulation for TS – Target Selection

Viswanathan A, Jimenez-Shahed J, Baizabal-Carvallo F. Jankovic J.
Stereotact Funct Neurosurg 2012;90:213-24



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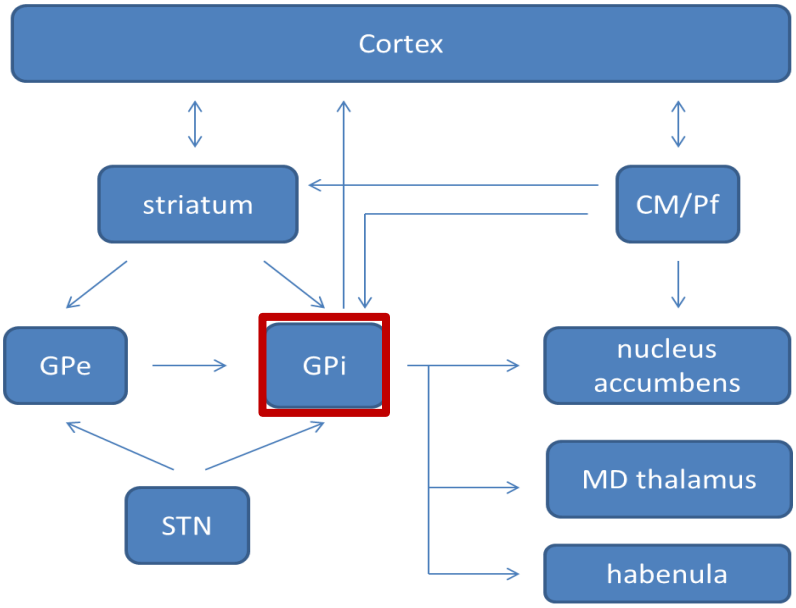
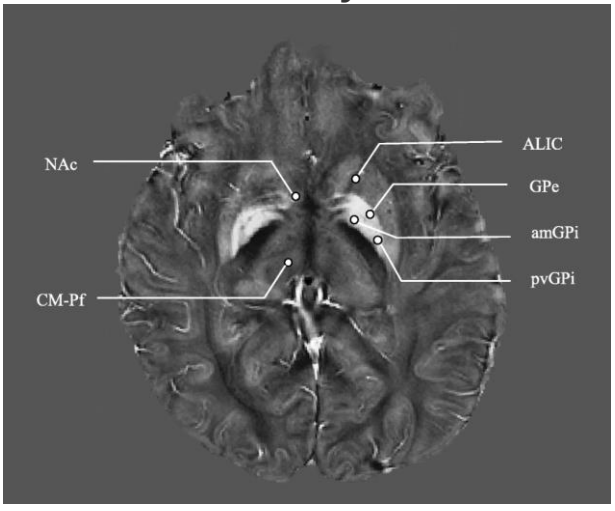


Possible targets proposed for DBS in Tourette syndrome



ALIC, anterior limb of internal capsule; amGPi, anteromedial or limbic GPi; CM-Pf, centromedian-parafascicular complex; GPe, Globus Pallidus externus; NAc, Nucleus Accumbens; pvGPi, posteroventral GPi.

Xu et al. Transl Neurodegener 2020;9:4

Bilateral globus pallidus stimulation for severe Tourette's syndrome: a double-blind, randomized crossover trial.

Kefalopoulou et al. Lancet Neurol 2015;14:595-605

- **Randomised, double-blind, crossover trial of GPi DBS in 15 patients with severe medically refractory TS (11 men, mean age 34.7 years; range: 25-55), 13 of whom completed all the blinded assessments.**
- **Mean YGTSS total score decreased from 87.9 (±9.2) at baseline to 68.3 (±18.6) during the on-stimulation assessment (p=0.048).**
- **The electrodes were placed under general anesthesia with MRI guidance into the anteromedial GPi (2 patients had posteroventral GPi placement).**
- **Modest improvement in mean YGTSS (6 patients had <10% improvement) and in video-based tic count, but no significant improvement in OCD measures, and 13% infection rate.**
- **The authors concluded that "GPi stimulation led to a significant improvement in tic severity, with an overall acceptable safety profile".**
- **This conclusion was largely based on 40.1% improvement in tics and improvements in the Beck Depression Inventory and in quality of life measurement during open-label phase of the study compared to baseline.**

The International Tourette Syndrome Deep Brain Stimulation Public Registry and Database

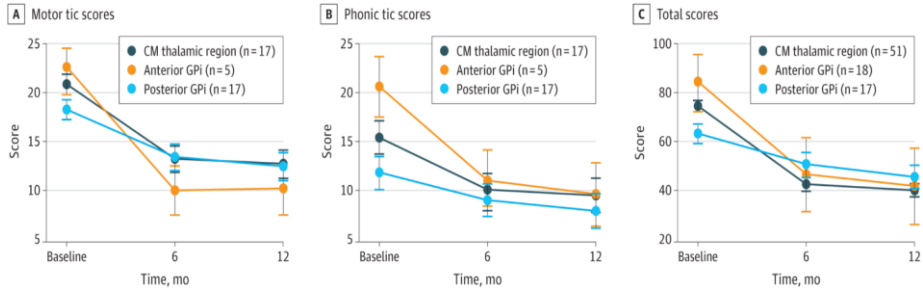
Martinez-Ramirez et al. JAMA Neurol 2018;75:353-9

- **185 patients (78% male; mean age at surgery, 29.1 years, range 13-58) with medically refractory TS who underwent DBS implantation from 2012-2016 at 31 institutions in 10 countries**
- **Implanted targets: centromedian thalamic region (57%), anterior globus pallidus internus (25%), posterior globus pallidus internus (15%), and the anterior limb of the internal capsule (3%).**
- **OCD present in 64% of patients and 22% had a history of self-injurious behavior.**
- **The YGTSS mean total score improved from 75.0 at baseline to 41.2 at 1 year after DBS implantation (p<.001); the motor and phonic tic subscores also improved significantly (both p<.001).**
- **The overall AE event rate was 35.4%, with intracranial hemorrhage occurring in 1.2% of patients, infection in 2.5%, and lead explantation in 1%; the most common stimulation-induced side effects were dysarthria (6.3%) and paresthesia (8.2%).**
- **Multiple brain targets resulted in similar suppression of tics.**

The International Tourette Syndrome Deep Brain Stimulation Public Registry and Database

Martinez-Ramirez et al. JAMA Neurol 2018;75:353-9

Yale Global Tic Severity Scale (YGTSS) Scores by Time and Brain Target

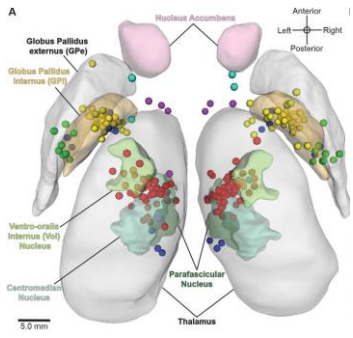


CM indicates centromedian; GPi, globus pallidus internus.

Image-based analysis and long-term clinical outcomes of deep brain stimulation for Tourette syndrome: a multisite study.

Johnson et al. JNNP 2019;90:1078-90

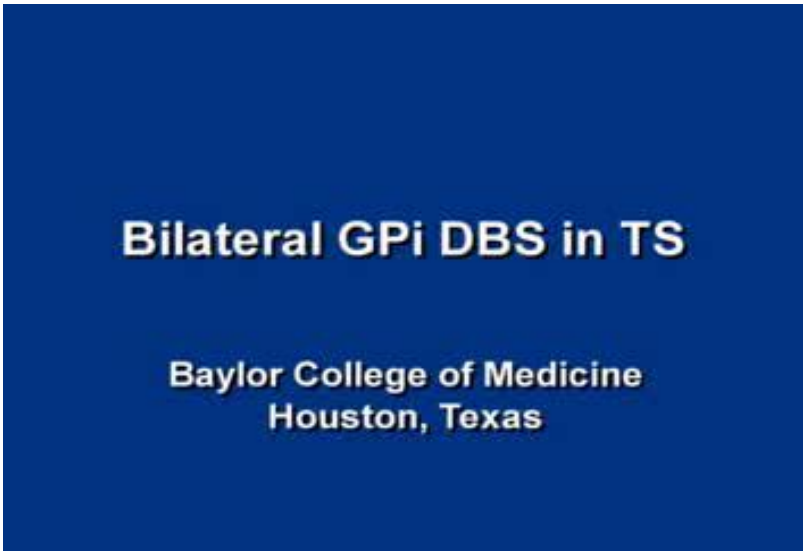
- **Retrospective clinical data and imaging from 13 international sites in 110 patients who were implanted in the centromedial (CM) thalamus (n=51), globus pallidus internus (GPi) (n=47), nucleus accumbens/anterior limb of the internal capsule (n=4) or a combination (n=8).**
- **Tics and obsessive-compulsive behavior (OCB) significantly improved over time (p<0.01).**
- **The median time was 13 months to reach a 40% improvement in tics.**
- **There were no significant differences across targets (p=0.84), presence of OCB (p=0.09) or age at implantation (p=0.08).**



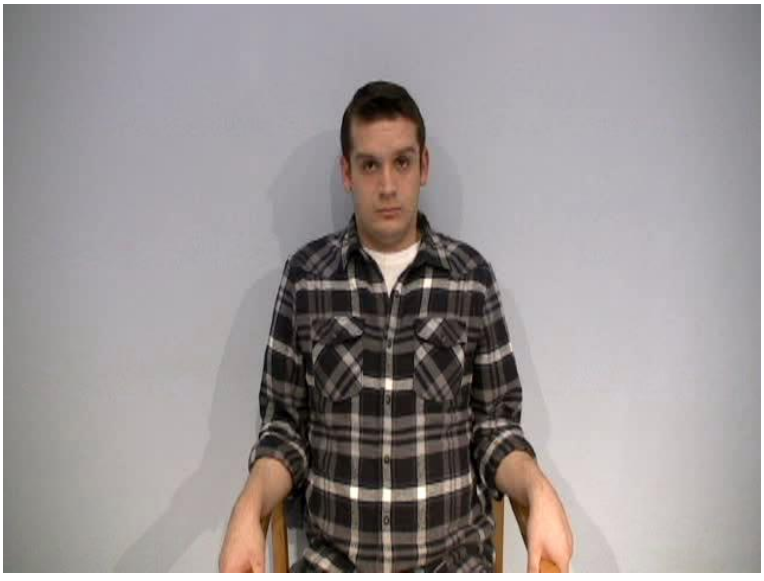
Muller-Vahl KR. JNNP 2019;90:1076-7

Bilateral GPi DBS in TS

Baylor College of Medicine



5 years after GPi DBS implantation



SPECIAL ARTICLE

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

Tamara Pringsheim, MD, MSc, Michael S. Okun, MD, Kirsten Müller-Vahl, MD, Davide Martino, MD, PhD, Joseph Jankovic, MD, Andrea E. Cavanna, MD, PhD, Douglas W. Woods, PhD, Michael Robinson, Elizabeth Jarvie, MSW, LCSW, Veit Roessner, MD, Maryam Oskoui, MD, Yolanda Holler-Managan, MD, and John Piacentini, PhD

Correspondence
American Academy of Neurology
guidelines@aan.com

Neurology® 2019;92:896-906. doi:10.1212/WNL.0000000000007466

SPECIAL ARTICLE

Comprehensive systematic review summary: Treatment of tics in people with Tourette syndrome and chronic tic disorders

Tamara Pringsheim, MD, MSc, Yolanda Holler-Managan, MD, Michael S. Okun, MD, Joseph Jankovic, MD, John Piacentini, PhD, Andrea E. Cavanna, MD, PhD, Davide Martino, MD, PhD, Kirsten Müller-Vahl, MD, Douglas W. Woods, PhD, Michael Robinson, Elizabeth Jarvie, MSW, LCSW, Veit Roessner, MD, and Maryam Oskoui, MD, MSc

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Neurology® 2019;92:907-915. doi:10.1212/WNL.0000000000007467

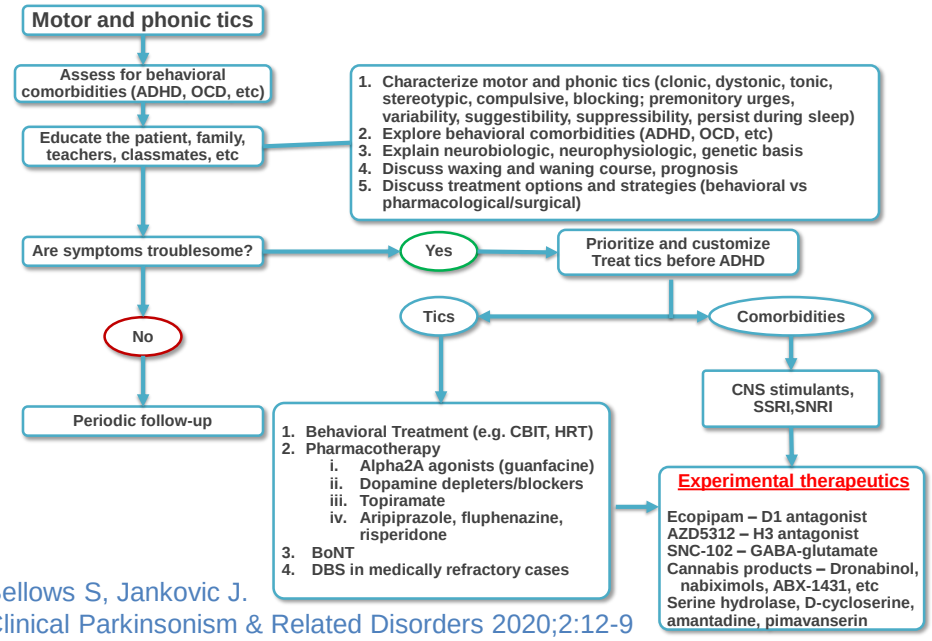
Practice Guideline: The treatment of tics in people with Tourette syndrome and chronic tic disorders

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

Pringsheim et al. Neurology 2019;92:896-906

- **Objective: To systematically evaluate the efficacy of treatments for tics and the risks associated with their use, and to make recommendations on when clinicians and patients should treat tics and how clinicians and patients should choose between evidence-based treatment options.**
- **Methods: In May 2016, a multidisciplinary panel consisting of 9 physicians, 2 psychologists, and 2 patient representatives was recruited to develop this guideline.**
- **Results: There was high confidence that the Comprehensive Behavioral Intervention for Tics was more likely than psychoeducation and supportive therapy to reduce tics. There was moderate confidence that haloperidol, risperidone, aripiprazole, tiapride, clonidine, onabotulinum toxin A injections, 5-ling granule and Ningdong granule were probably more likely than placebo to reduce tics. There was low confidence that pimozide, ziprasidone, metoclopramide, guanfacine, topiramate, tetrahydrocannabinol, and deep brain stimulation of the globus pallidus were possibly more likely than placebo to reduce tics.**

Treatment Algorithm for Tourette Syndrome



Bellows S, Jankovic J.
Clinical Parkinsonism & Related Disorders 2020;2:12-9

Mozart's movements and behaviour: a case of Tourette's syndrome?

Aidin Ashoori, Joseph Jankovic

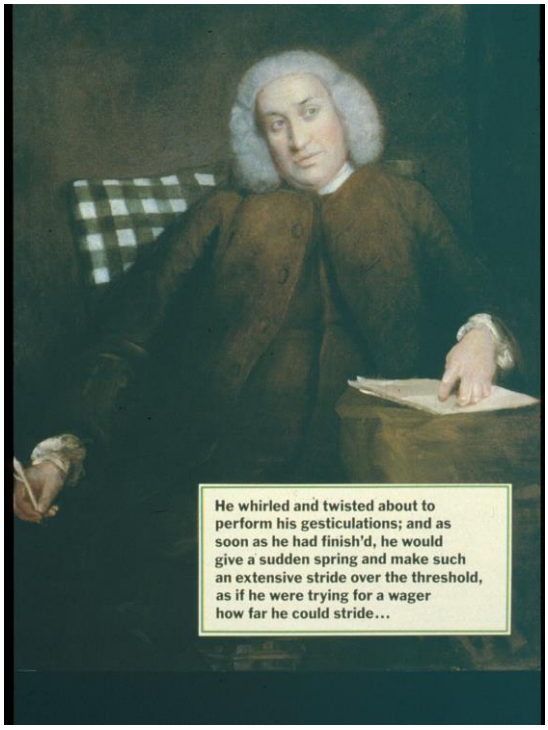
J Neurol Neurosurg Psychiatry 2007;**78**:1171–1175. doi: 10.1136/jnnp.2007.114520

In this review, we intend to explore the often asked question: "Did Mozart have Tourette's syndrome?" Although there are numerous reports attributing Mozart's peculiar personality and behaviour to a spectrum of neurobehavioural disorders such as Tourette's syndrome, autistic disorder, Asperger's syndrome, attention deficit hyperactivity disorder, obsessive–compulsive disorder and paediatric autoimmune neuropsychiatric disorders associated with streptococcal infection, the evidence for any of these disorders is lacking. Whether Mozart's behaviour was nothing more than a reflection of his unique personality or a more complex neurological disorder, aggravated later in life by enormous demands by his father and society, his behaviour has been the subject of many biographies. It will also remain unknown to what extent his accomplishments and failures were shaped by his childhood experiences, pressured lifestyle, and his innate genius and extraordinary talent. Lessons from his life may have important implications for other gifted individuals and savants whose special attributes may lead them to succeed or, on the other hand, suppress their emotional growth and make them more vulnerable to stress and failure.

The 250th anniversary of the birth of one of the greatest musical geniuses of all times, Wolfgang Amadeus Mozart (1756–1791), provides an opportunity not only to reflect on his immeasurable contributions to the world of classical music, but also to examine him as a man of exceptional creative power. Mozart's biographical accounts often comment on his peculiar behaviour which has been interpreted by some as a manifestation of an underlying neurobehavioural disorder, such as Tourette syndrome (TS). Once considered a rare psychiatric syndrome.[7 8] Various structural and functional imaging studies of brains of musicians have found that in contrast with non-musicians, the musicians' brains tend to have increased gray matter in Broca's area and in certain portions of the auditory cortex, such as the Heschl's gyrus and planum temporale.[9 10] Studies of developmental and acquired disorders of musical listening and interpretation have shown that brain plasticity is involved in musical perceptions and integration with cognitive and emotional responses,[11] and that music could have both evocative and suppressive effects on some patients with movement disorders such as TS and parkinsonism.[12]

Although many individuals with unique talents have been carefully studied, no unified theory has emerged to explain the neurological basis of such exceptional creative or interpretive abilities, as demonstrated by some people with autism or some savant artists. It is beyond the scope of this review to discuss the neurobiology of savant and the reader is referred to other sources,[13 14] but the brain mechanisms giving rise to savant-like features may be relevant to the understanding of the neurobiology of a genius mind, such as that of Mozart. Whether savant is more frequently observed in patients with TS or whether some savant cases manifest features of TS, such as tics and OCD, has not been systematically studied.

Insanity and exceptional musical talent have often been thought to be linked, but the mechanism of this relationship is unknown.[15] As an example, David Helfgott, a prodigious pianist featured in the movie "Shine," has been thought to suffer from a mild form of schizophrenia with positive symptoms. He grunts, mutters, sings, talks to himself very loudly and exhibits other tic-like mannerisms as he plays.[16] Creativity has often been associated with bipolar disorder and some composers, artists, authors and



Dr. Samuel Johnson

Movement Disorders
CLINICAL PRACTICE

LETTERS: NEW OBSERVATIONS

Perceived Worsening of Tics in Adult Patients with Tourette Syndrome after the COVID-19 Outbreak

David Mataix-Cols, PhD,[1,2]* Helene Ringberg, MSc,[2] and Lorena Fernández de la Cruz, PhD[1,2]

To our knowledge, there are no data on the perceived impact of the COVID-19 outbreak on tic severity in persons with Tourette syndrome (TS) or chronic tic disorder (CTD), although experts have warned of a potential exacerbation of symptoms.[1] As part of an ongoing global survey of driving experiences among adults with TS/CTD, we included the question: *Do you feel that your tics have worsened since the start of the coronavirus pandemic (since February–March 2020)?* Responses were recorded on a 5-point Likert scale ranging from "My tics have become much worse" to "My tics have become much better." Participants could expand their answers in an open field. Importantly, they were unaware that they would be asked a question about COVID-19. Data collection took place between April 27th and May 26th 2020.

Participants included 178 adult individuals with a diagnosis of TS/CTD (57% women, 40% men, 2% other/prefer not to say; 44% 18–25 years of age, 26% 26–35 years of age, 13% 36–45 years of age, 11% 46–55 years of age, 6% ≥56 years of age). Most participants were located in Europe (58%) or North America (35%). The majority (74%) reported psychiatric comorbidities, including anxiety disorders (43%), obsessive–compulsive disorder (35%), depression (34%), attention-deficit/hyperactivity disorder (33%), and autism spectrum disorders (10%). The mean tic severity, according to the Adult Tic Questionnaire (ATQ),[2] was 52.81 (SD = 32.46; motor tics scale: 34.83, SD = 18.14; vocal tics scale: 17.98, SD = 16.77).

Approximately half of the participants (48%) experienced that their tics were a little (33%) or much worse (16%) since the outbreak. Analysis of the open field revealed some frequent themes. Perceived tic worsening was associated with: increased stress and anxiety because of worries about finances, future and family, confinement and lack of physical exercise/activity, fewer distractions, change or lack of routines, having to go to work, and being exposed to the public. Some individuals reported perceived stigma regarding coughing tics, increased tics because of wearing masks, and an increase of self-injurious behaviors.

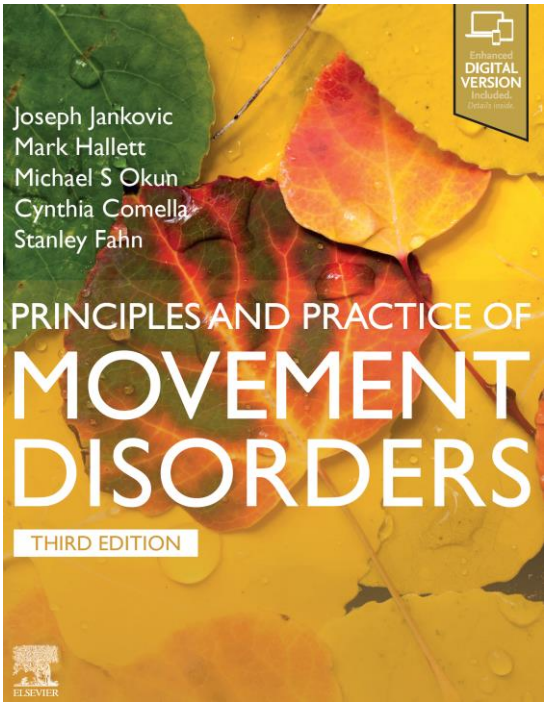
Another 44% of the participants reported that their tics remained unchanged. The remaining reported their tics to be a little (6%) or much better (2%). These individuals reported that working from home and limiting social contact resulted in reduced stress and tic severity.

Follow-up analyses explored whether perceived worsening of tics was associated with sociodemographic and clinical variables. Compared to participants whose tics remained unchanged or improved, participants experiencing a worsening of symptoms were more likely to be younger ($\chi^2 = 14.08$, $P = 0.007$, with significant pairwise differences for the group 18–25 years of age vs. older groups) and have more severe tics (ATQ mean difference: −12.07, $t = -2.52$, $P = 0.013$; motor scale: −6.80, $t = -2.54$, $P = 0.012$; vocal scale: −5.26, $t = -2.11$, $P = 0.036$). Psychiatric comorbidities or deaths per capita attributed to COVID-19 in the country of origin were not associated with a perceived worsening of tics.

Despite the limitations of the subjective reporting of tic severity,[3] a substantial proportion of patients with TS/CTD have perceived a worsening of their tics since the outbreak of the pandemic. These individuals may need additional support during these challenging times.

Author Roles

(1) Research project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C.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Parkinson's Disease Center and Movement Disorders Clinic

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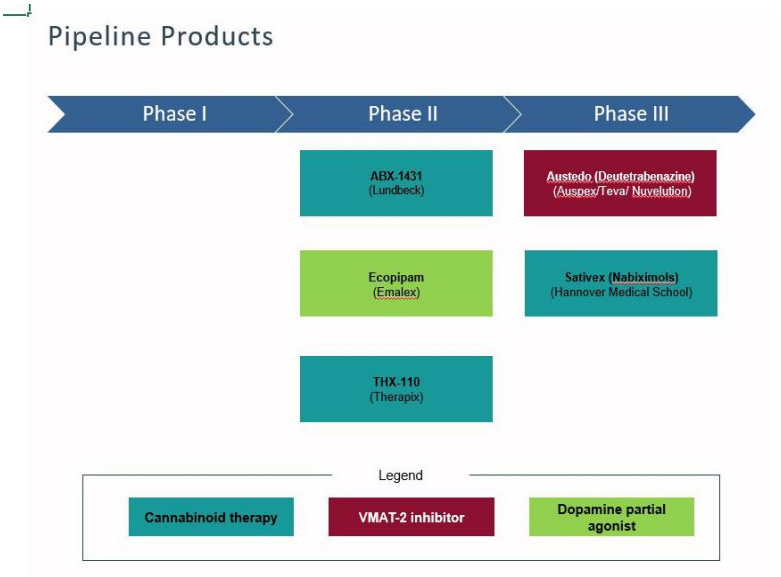
THANKS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