Tics and Tourette syndrome (TS)

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Disclosures

- My spouse/partner and I have the following relevant financial relationship with a commercial interest to disclose:

Tourette Association of America (TAA)	Medical Advisory Board
Psychiatry Education Forum LLC	Speaker
MGH Psychiatry Academy	Speaker

Learning Objectives

Following this activity, the participants should be able to:

- 1. Cite the criteria used to diagnose Tourette syndrome (TS) and other tic disorders.
- 2. Describe the common co-occurring conditions with TS.
- 3. Describe the range of effective management and treatment strategies.

What are tics?

- Sudden, brief, recurrent, non-rhythmic, stereotyped, movements and/or sounds
- “Unvoluntary” – irresistible urge - like a terrible itch, or a sneeze or yawn

- “Jump” - location, frequency, type, complexity
- Wax and wane
- Highly suggestible
- Preceded by “premonitory urge”
  - Sensory-type feeling temporarily relieved by performing tic
- Impacted by <u>modifying factors</u>

Mills et al., 2014

Hallett 2015

Four-way Tic Chart

Motor

- Simple
  - Eye blinks
  - Nose twitches
  - Grimaces
  - Shoulder shrugs
  - Head, arm or leg jerks
- Complex
  - Coordinated movements of multiple muscles
  - Complex Gestures/Postures
  - Echopraxia (mimicking others)
  - Poking/pinching/punching
  - Touching/tapping/rubbing

Phonic

- Simple
  - Sniffing
  - Coughing
  - Throat clearing
  - Grunting
  - Barking/animal sounds
- Complex
  - Complex utterances
  - Words
  - Phrases
  - Echolalia (repeating others)
  - Palilalia (repeating oneself)
  - Coprolalia ~15% !!

Modifying Factors of Tics

ASSOCIATED WITH TIC REDUCTION

- Relaxation
- Intense concentration/”Flow”
- Acting/singing
- Sleep
- Alcohol
- Being in presence of the doctor

ASSOCIATED WITH TIC WORSENING

- Anxiety/Stress
- Frustration
- Boredom
- Fatigue / Tiredness
- Social situations
- Excitement
- Homework
- Anticipation
- Illness

What is Tourette Syndrome?

- Childhood-onset neuropsychiatric disorder characterized by tics
  - Prevalence about 0.5-1%
    - Estimated between 0.3% and 0.9% (Scharf et al 2015)
- Criteria:
  - At least 2 motor and 1 vocal tic over the course of the illness
  - At least one-year duration, though the tics can wax and wane in frequency
  - Onset before age 18
  - Not secondary to a substance or another medical condition

Other Tic Disorders

- Persistent (Chronic) Motor or Vocal Tic Disorder:
  - Same criteria as TS, but only motor OR vocal tics
  - Additional 1-2% of children

- Provisional Tic Disorder
  - Any number of motor/vocal tics, less than 1 year in duration
  - Part of typical development? (~20-25% of kids)
    - Recent study where resolution of provisional tic disorder is exception rather than rule… (Kim et al (2019) Scientific Reports)

TS Epidemiology

- Male > Female predominance (~3.5:1)
- Mean age of onset of tics is ~5 to 7 years
- Maximum severity typically in early adolescence

- High rates of co-occurring conditions
- “Disorder of disinhibition”
  - Emotions, thoughts, vocalizations, actions

Heritability

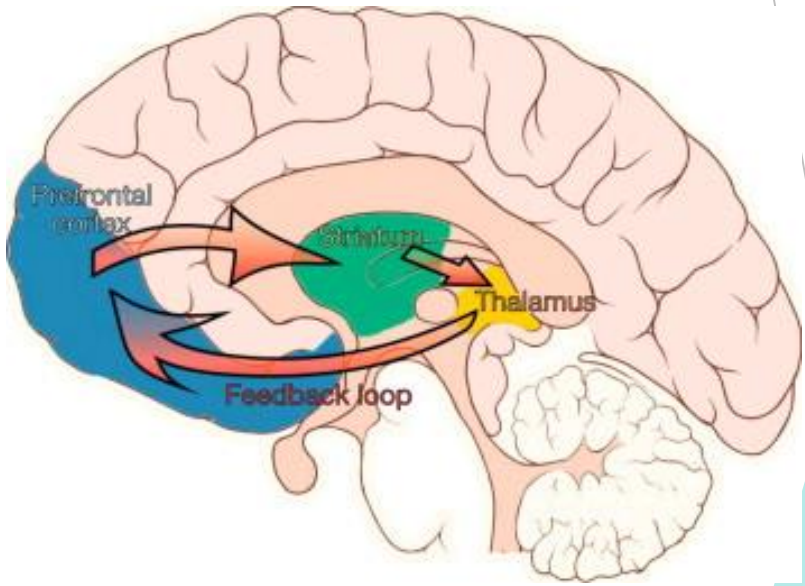
- Complex inheritance pattern, very familial
  - Heritability estimates ~80-90%
  - Genetic and non-genetic risk factors
- Genome-wide association (GWAS) data suggest TS is polygenic
  - More likely 2o to common polymorphisms vs. rare mutations
- Genetically associated with OCD, and ADHD
  - Cross-disorder endophenotypes: “disinhibition endophenotype” and “symmetry endophenotype”

TSAICG, Am J Hum Genet 2017
Darrow et al, AJP, 2017

Neurocircuitry of Tourette syndrome (TS)

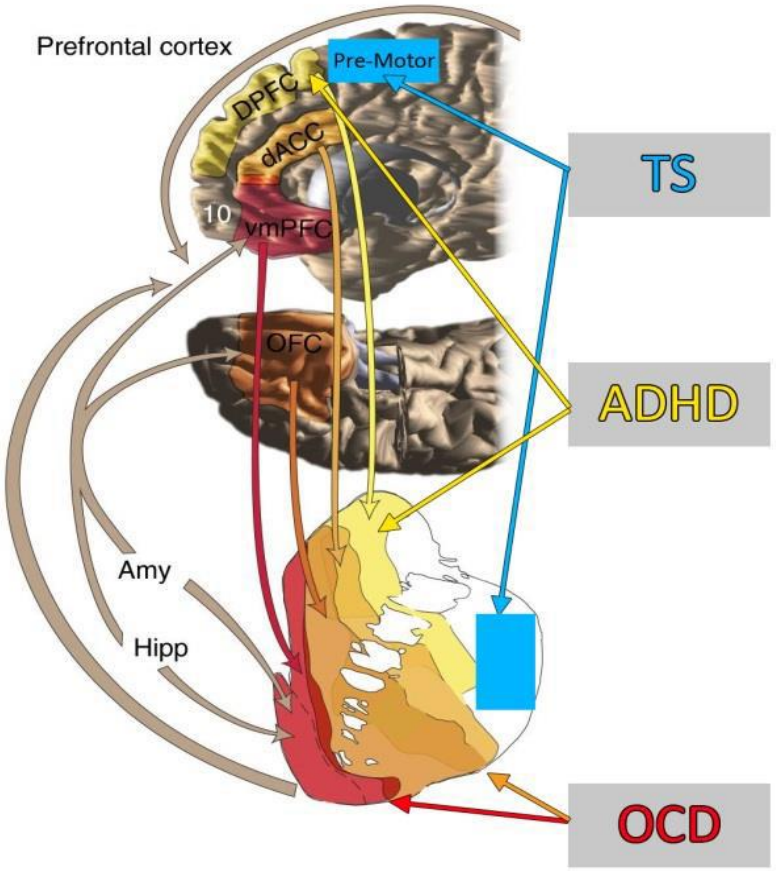
(Dysfunction of frontocortical-striatal-thalamo-cortical (CSTC) circuitry networks)

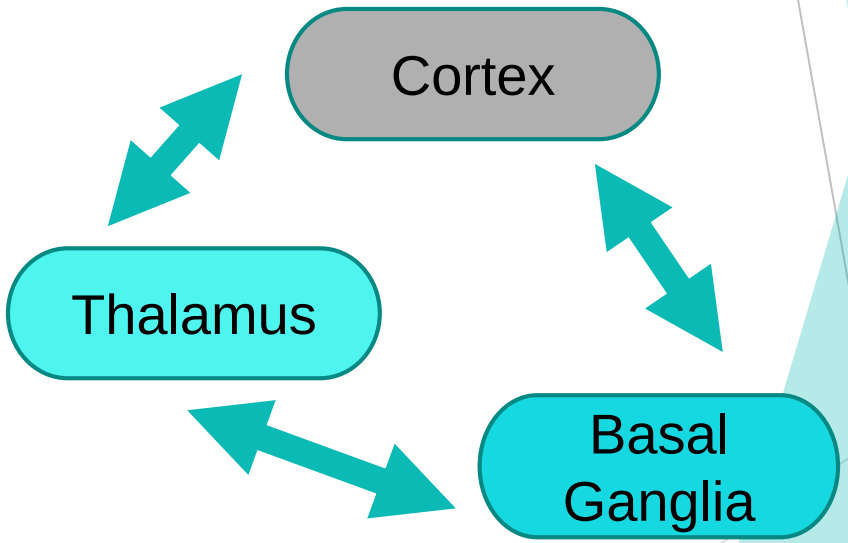
- Associated with habit formation, affect regulation, reward processing, inhibitory control
- Leads to **disinhibition and dysregulation** of motor (movement), cognitive (thinking), affective (emotion), motivation (reward-based) processes
- Difficulties with impulsivity and compulsivity
- Clinical manifestations: Tics, OCD, ADHD, executive dysfunction, mood dysregulation, hair-pulling/skin-picking, etc.
- Neurotransmitters: Glutamate, Dopamine, Serotonin, GABA



Beddows 2015 - http://scitechconnect.elsevier.com/neurobiology-basis-of-ocd/.
Modified from original image, credits: Patrick J. Lynch and C. Carl Jaffe.

Tourette Pathophysiology: Dysregulated Cortico-striatal-thalamo-cortical (CSTC) Networks





Modified from Adapted from Haber & Knutson, 2010

Prevalence of Other Psychiatric Disorders in TS

- Co-occurring diagnoses: 85% (!!)
  - Obsessive-compulsive disorder: >50% (more female)
  - ADHD: >50% (more male)
  - OCD or ADHD: ~70% OCD and ADHD: ~30%

- If OCD: more likely to see anxiety, mood conditions, ADHD/oppositionality
- If ADHD: more likely to see anxiety, oppositionality, intermittent explosive disorder
- More severe tics generally associated with increased co-occurring conditions

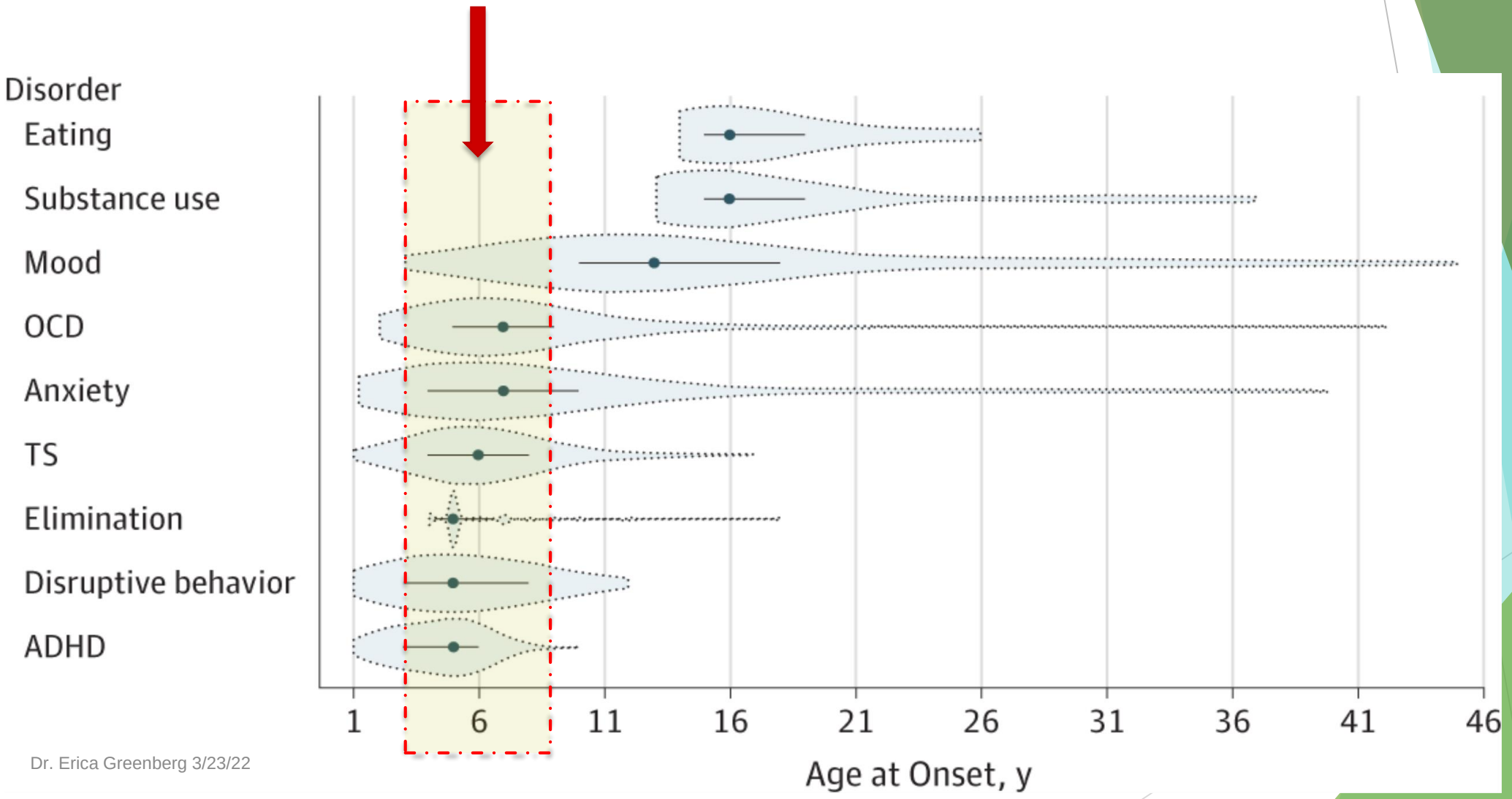
Hirschtritt et al 2015

Rates of Other Psychiatric Disorders in TS

- Mood, non-OCD anxiety, oppositional defiant disorder: ~30%
- Intermittent explosive disorder: ~25%
- Autism spectrum disorder (ASD) symptoms: ~25%
  - Likely confounded by tic/OCD overlapping symptoms
- Body-focused repetitive behaviors (BFRBs)
  - Hair pulling disorder (trichotillomania): 4%
  - Skin picking disorder: 13%

Hirschtritt et al 2015
Ganos and Martinos 2015
Greenberg et al 2017
Darrow et al 2017

4-10 Yrs. Old
peak risk



(Hirschtritt et al. 2015; *JAMA Psychiatry*)

Clinical Course

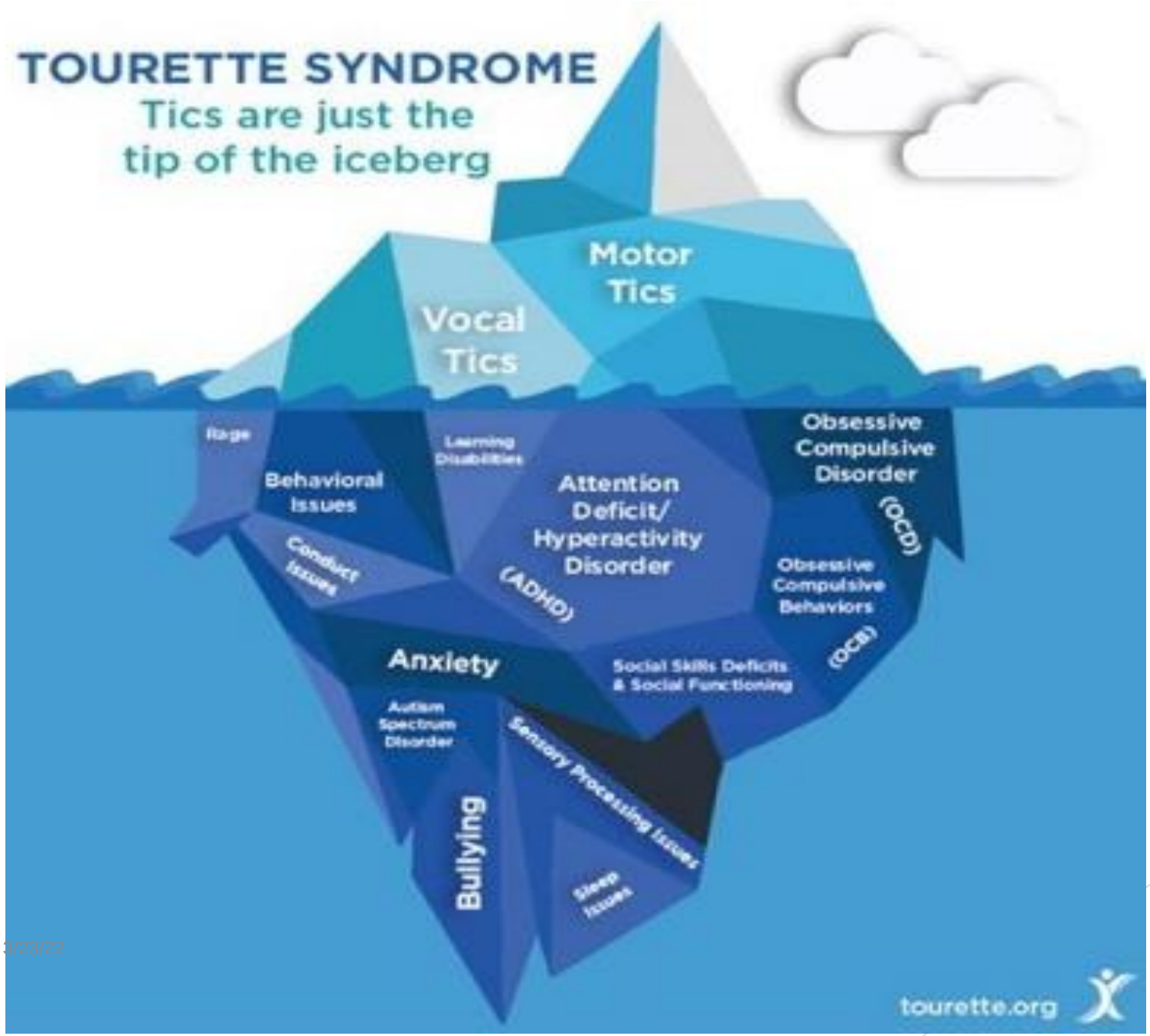
- General rule regarding clinical course:
  - Rule of Thirds: by late adolescence/early adulthood 1/3 “resolve,” 1/3 improve, 1/3 remain; ~10% of patients have persistent, disabling symptoms
- In Tourette syndrome:
  - Simple before complex; motor before phonic; proximal/rostral to distal/caudal (i.e., “top to bottom”)
- Sexual dimorphism? Baizabal-Carvallo JF, and Jankovic J (2022). Sex differences in patients with Tourette syndrome. CNS Spectrums https://doi.org/10.1017/S1092852922000074

Table 2

Sex differences summary: Brief summary of evidence of differences of clinical characteristics of TD in girls and women compared to boys and men.

Clinical Characteristic	Difference in Girls and Women
Age of tic onset	May be later
Peak tic symptom severity	Later
Tic remission	Less likely; increased tic severity is more common in women
Tic complexity	May be more complex
ADHD	Less common
Learning disabilities	Less common
OCD	More common
Mood and other anxiety disorders	More common
Psychosocial impairment	Worse, and worsens with age
Perinatal stress	May be less common
Alterations in corpus callosum, frontoparietal cortex, and putamen asymmetry	Not reproduced in female cohorts
Response to anti-androgenic medication	May be less likely
Response to haloperidol	More likely

Garris J and Quigg M, 2021, Neurosci & Biobehavioral Reviews


TOURETTE SYNDROME
Tics are just the tip of the iceberg
Motor Tics
Vocal Tics
Rage
Behavioral Issues
Learning Disabilities
Attention Deficit/ Hyperactivity Disorder
(ADHD)
Conduct Issues
Obsessive Compulsive Disorder
(OCD)
Obsessive Compulsive Behaviors
(OCB)
Anxiety
Social Skills Deficits & Social Functioning
Autism Spectrum Disorder
Sensory Processing Issues
Bullying
Sleep Issues
tourette.org

Impact on Life

- >2/3 children: impaired peer relations, difficulties with friendships
  - Quality of life significantly worse compared to normative sample
- Suicidal Ideation/Self-Harm in Children and Adolescents with Tic Disorders
  - 32% youth (from parent report)
  - 51% of adults
- Of those whose parents reported suicidality, biggest challenges:
  - Co-morbidity
  - Feeling discriminated against
  - Negative impact of tics on school experience (>90%)

(Cruz et al, 2019 AACAP)

Impact on Life Continued

- TS Treatment: Parent Reports of Trials and Tribulations
  (Parents' perceived effectiveness of treatments for TS and co-occurring conditions)
  - 42% parents said biggest challenge is "dealing with co-occurring conditions"
  - 20% said biggest challenge is "lack of effective medications/treatments"
    - 33% reported children with adequate symptom control from medication
    - 30% of children and adults with TS have tried **5 or more** medications

(Cruz et al, 2020, AACAP abstract)

When to Treat Tics?

Tics/urges cause physical **pain/impairment**

Tics cause significant **social/functional problems**

Tics cause **psychological distress**

Types of Treatment

- Behavioral
  - Comprehensive Behavioral Intervention for Tics (CBIT)
    - ?Mindfulness strategies
- Pharmacological

Overall Treatment Guidelines

- Reduce tic severity and frequency (vs cure)
- Manage the co-occurring conditions
  - Intensity of tics does not have to equate with impairment
- New 2019 American Academy Neurology (AAN) Guidelines + New 2021 European Clinical Guidelines

Behavioral Interventions

- CBIT: Comprehensive Behavioral Intervention for Tics
  - Components
    - Habit Reversal Training (HRT)
      - Awareness, competing response, social support
    - Function-based Intervention
      - Contextual factors that support or maintain expression
  - Meta-analysis for behavioral therapy in TS showed medium to large effect size (McGuire et al. 2014) – children and adults
- Other behavioral treatments options?
  - Mindfulness-based approach (Reese et al 2021 Pilot and Feasibility Studies)
  - Symptom combination targeting approach (Modified CBIT)

Pharmacotherapy

- Only FDA approved treatments: Pimozide, Haloperidol and Aripiprazole
  - Majority of treatments used off-label
  - Few randomized control trials (RCT)
    - Informed decisions are limited/based on expert consensus
- Lots of current studies, **increased hope**! (But currently, limited new…)
- Three tiers:
  - Tier 1: Alpha-2 agonists (clonidine, guanfacine, extended-release clonidine)
  - Tier X: NEW MEDICATIONS HERE

  - Tier 2: Atypical neuroleptics (risperidone, aripiprazole, etc.)
  - Tier 3: Typical neuroleptics (haloperidol, pimozide, etc.)

Daily Doses of Frequently Prescribed Medications

Medication	Range of daily dosing
Haloperidol	0.25-4.0mg
Pimozide	0.5-8.0mg
*Risperidone	0.125-3.0mg
Aripiprazole	1.0-15.0mg
*Clonidine	0.025-0.4mg
*Guanfacine	0.25-4.0mg

Egolf, A. Coffey, B. Current Pharmacotherapeutic Approaches to the Treatment of Tourette Syndrome: Drugs Today; 2014 Feb; 50 (2):159-79 (Adapted from Coffey Slides 2020)

Pharmacotherapy Continued

- Large gap in tolerability and effectiveness between Tier 1 and Tier 2
- Commonly-used off-label agents for Tier 1b
  - Topiramate – some evidence, for use in mild/moderate symptoms
  - Ziprasidone – non-inferior per meta-analysis with other D2 blockers
  - Fluphenazine – high potency D2, but with ?fewer side effects
- Other new agents?

Pharmacology – New Agents - Promising

- Ecopipam: Selective antagonist of Dopamine 1 receptors
  - Promising Phase 2b trial, multi-site study concluded, awaiting results
  - Well-tolerated and reduced tics in preliminary (Gilbert et al 2018)
- Endocannabinoids:
  - THC (dronabinol) in early 2000s studies showed some benefit
  - Recent trial with mixed cannabinoids in adults met primary end-point significant improvement in symptoms
  - Ongoing trials: CANNA-TICS; https://tourette.org/research-medical/medical-marijuana-research/
- 5-Ling and Ning-dong granules: Herbal compounds
  - Approved treatment for tics in China (equivalent to tiapride); studies in US underway

Billnitzer and Jankovic (2020) Neurotherapeutics

Pharmacology – New Agents – Less Promising

- Valbenazine, Deutetrabenazine: Vesicular monoamine transporter type 2 (VMAT2) inhibitors
  - Both negative for primary end-point
  - YGTSS-total tic severity reduction favored deutetrabenazine over placebo

- NAC: (Bloch et al 2016) No significant difference between NAC and placebo for primary/secondary outcome

Billnitzer and Jankovic (2020) Neurotherapeutics

Endocannabinoids and Tourette Syndrome?

- Endocannabinoid system plays a role in **motor inhibition**
  - Highest density of **central cannabinoid (CB1**) receptors: areas implicated in pathophysiology of TS
- Evidence suggests **delta THC increases intra-cortical inhibition**
  - THC may *reduce* central TS disinhibition through modulation of neurotransmitters
  - Two early RCTs (2002; 2003) by Dr. Kirsten Muller-Vahl in 36 adults with TS: dronabinol was more effective than PBO in tic reduction

Adopted from Coffey 2020 Slides

American Academy of Neurology (AAN) 2019 Treatment guidelines

- Comprehensive Behavioral Intervention for Tics (CBIT) should be initial treatment
- Psychoeducation to family and schools
- Assess for and treat co-occurring conditions

- Pharmacologically:
  - Clonidine and guanfacine are *probably* and *possibly*, respectively, more likely reduce tic severity vs placebo
    - Alpha agonists more effective in those with tics and ADHD compared to those with tics without ADHD
  - Haloperidol, risperidone, aripiprazole, tiapride are *probably* more likely than placebo to reduce tic severity
  - Pimozide, ziprasidone and metoclopramide are *possibly* more likely than placebo to reduce tic severity

Pringsheim, et al. 2019 *Neurology*
Roessner et al 2021 Eur Child & Adol Psychiatry

European Clinical Guidelines

- Supported AAN Conclusions:
  - **Strong confidence** for behavioral approach
  - "....**moderate confidence** that haloperidol, risperidone, aripiprazole, tiapride, clonidine, Botox injections, 5-ling granule, and Ningdong granule were probably more likely than placebo to reduce tics...."
  - **Lower confidence** for pimozide, ziprasidone, metoclopramide, guanfacine, topiramate, and THC"
- No hierarchical recommendation…
  - Survey shows aripiprazole is most often used agent for pharmacological TS treatment

Roessner et al 2021 Eur Child & Adol Psychiatry

Part 2: Additional Specific Areas of Interest

- Impact of co-occurring conditions
  - Tourettic OCD
  - Intrusive Destructive Behavior (IDB)
  - Tics and ADHD
- Recent increase in tic-like behaviors / COVID-19 Impact
- Tics and Inflammatory Processes

Obsessive-Compulsive Disorder (OCD) in TS

- DSM-5: Obsessive-compulsive and Related Disorders category
- Diagnostic criteria:
  - Obsessions and/or compulsions; at least 1h a day; moderate distress and/or impairment in functioning
- Specify if co-occurring tics
  - **~25% in those with childhood-onset OCD**

Does “Tic-related OCD” differ from non-tic-related OCD?

- **Yes!**
- More common in pediatric-onset OCD (vs adult onset)
- Often associated with particular sets of OCD symptoms:
  - Subtypes: Symmetry (associated with NJR) and Forbidden thoughts
  - **Obsessions**: symmetry, aggression, sexuality, religiosity
  - **Compulsions**: checking, touching, re-writing, evening-up, symmetry
    - “Not just right”
- “Tic-related OCD” more similar to TS than OCD

“Tourettic OCD”
(coined by Mansueto et al 2005)

- Associated with:
  - Male sex, earlier OCD age of onset, more OCD impairment
  - Early sensory hypersensitivity
  - Attentional difficulties, learning disorders, impulsivity
  - Skin picking / other body-focused repetitive behaviors
  - Increased anxiety disorders and depression symptoms

- Not-just-right feelings
  - Describe sensory phenomena / feeling of incompleteness driving symptoms
  - Not *afraid* of something bad happening, afraid they “**will explode**”
  - Limited response to fear-based exposures (ERP)

Mansueto and Keuler 2005
Ferrao et al 2009

Does it matter? YES!

- May need combination of OCD-targeting AND tic-targeting pharmacological treatment
- Sensory/not-just-right compulsions may benefit from ‘distress tolerance’ (vs fear-based exposure) component in behavioral therapy

Impact on pharmacological treatment?

- OCD (and co-occurring tics)
  - Behavioral treatment equally effective
  - Serotonergic agents (SSRIs, clomipramine) *perhaps* less effective
    - NOT the case for everyone, but lower threshold to consider combined treatments
  - Medication augmentation strategies
    - **Antipsychotic*: Aripiprazole, Risperidone, Ziprasidone, Haloperidol, Fluphenazine
    - *Glutamate modulating agent*: Memantine, N-acetylcysteine, Lamotrigine, Topiramate
    - *Alpha-agonist?* (e.g. guanfacine, clonidine)

Differentiating Symptoms

- To help distinguish between tics and compulsions, ask: “what is driving the behavior?” Thought/anxiety or a Feeling/sensation?
  - Unpleasant thought/anxiety (obsession) ➔ Compulsion
  - Unpleasant feeling/sensation (premonitory urge) ➔ Tic
- Not uncommonly, something in the middle…
  - Ticculsion: Thought/anxiety driving a tic-like movement
  - Tourettic compulsion (or tic-related OCD, or Tourettic OCD): Sensory/not-just-right feeling driving a compulsion

Intrusive-destructive behaviors (IDBs): Reported experiences in those with combination of symptoms

- Described by subset of individuals with tic disorders (and most often co-occurring OCD, ADHD/executive dysfunction) who feel *compelled to perform certain behaviors despite awareness of negative implications*
  - Experience intrusive thoughts of behaviors they don't want to do, but then feel compelled to do
  - Behaviors are simultaneously *deliberate*, *satisfying* and *upsetting*
    - Properties of tic, intrusive thought obsession/compulsion, impulse/disinhibition
  - Driven by extent of the potential negative consequence
- Examples: Pushing on a bruise; Knocking down constructed creation; Licking dirty sink; Breathing in air while swimming
- Treatment involves combination of educational and evidence-based tic, OCD and ADHD behavioral and medication treatment approaches

Greenberg et al 2021

Attention Deficit Hyperactivity Disorder (ADHD)

- Associated challenges with ADHD+TS
  - Worse quality of life, increased social difficulties, increased ADHD-related symptoms/impairment
- Treatments
  - Pharmacological management:
    - Stimulants, alpha-agonists (e.g. clonidine, guanfacine), atomoxetine, etc.
  - Behavioral management
- Treatment Considerations
  - Stimulants with tics?
  - Modified behavioral treatment approach?

TS and ADHD Pharmacotherapy

- Stimulants in patients with tics had traditionally been avoided
  - Large meta-analysis by Cohen et al (2015)
    - No difference in tic onset or worsening in stimulant vs. placebo group
- Treatment of ADHD and Tics (TACT) Study: Tic and ADHD symptom reduction / side effect profile best with stimulant / alpha-agonist combo
  - No observed tic worsening with stimulants(!)
- Recent Cochrane Review (next slide)
- If problematic tics and ADHD symptoms, can try alpha-agonist first or switch to atomoxetine
  - Alpha-agonists more effective when co-occurring ADHD
  - Better for hyperactivity/impulsivity (vs inattention)

Cohen et al. (2015) J Am Acad Child Adolesc Psychiatry
Tourette Syndrome Study Group (2002). Neurology.
Osland, Steeves, Pringsheim. 2018. Cochrane Review

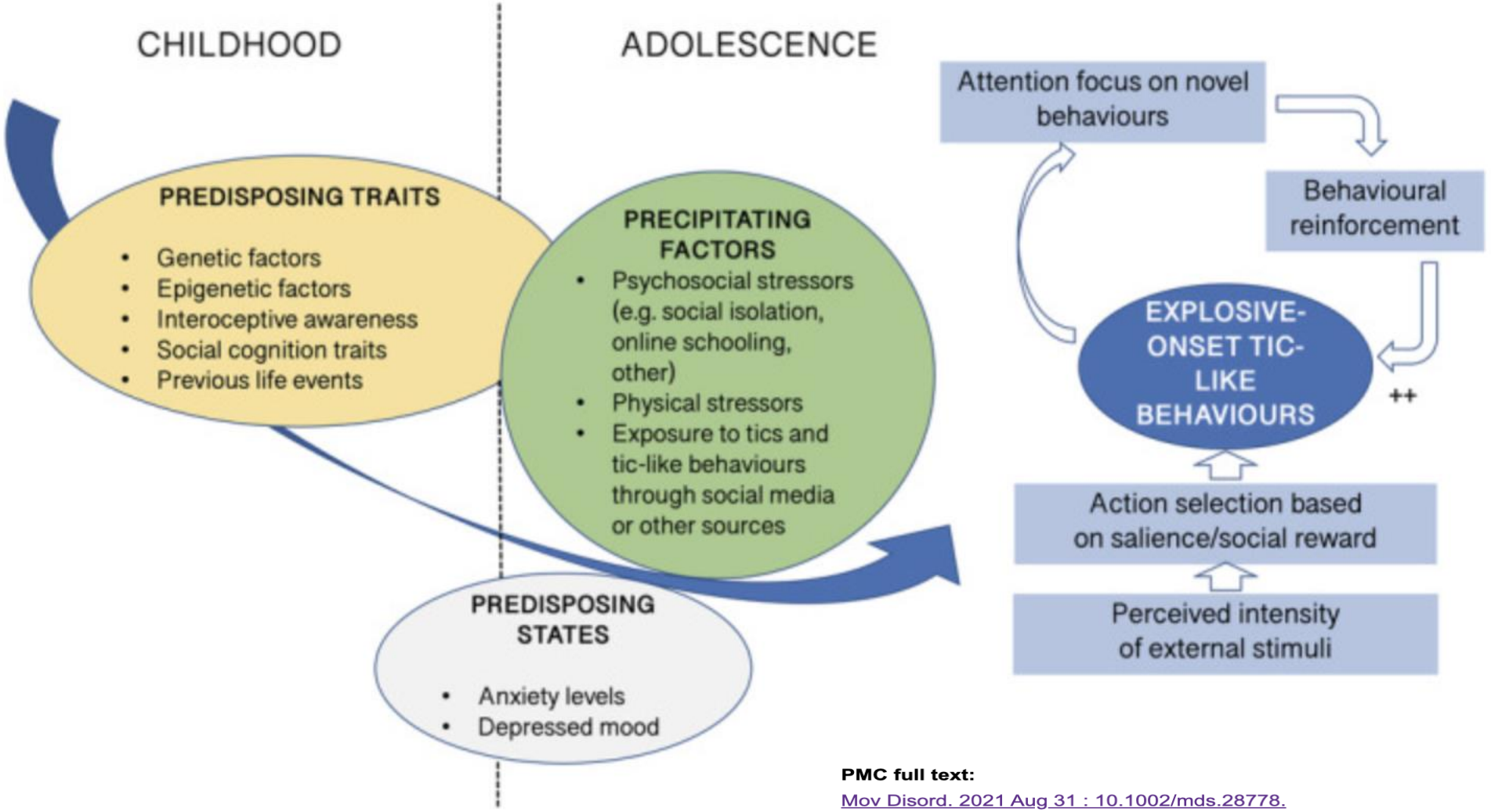
Recent Cochrane Update: Continued

- Worsening:
  - High-dose dextroamphetamine exacerbated tics (1 study)
- Conclusions:
  - Methylphenidate, clonidine, guanfacine, desipramine, atomoxetine reduce **ADHD** symptoms in youth with tics and ADHD
  - Guanfacine, methylphenidate, clonidine, methylphenidate + clonidine, and desipramine reduce **Tic** symptoms in youth with tics and ADHD
    - Desipramine was beneficial, but worse risk/benefit ratio
  - Given methodological difficulties, no evidence-based recommendations when choosing

Osland, Steeves, Pringsheim. 2018. Cochrane Review
Malmivaara. 2020. Dev Med and Child Neur

COVID 19 Impact?

- **Helpful resources:**
  - TAA Statement: Rising Incidence of Functional Tic-Like Behaviors
  - McGuire et al (2021) "Distinguishing and Managing Acute-Onset Complex Tic-like Behaviors in Adolescence" *JAACAP Letters to the Editor.* https://doi.org/10.1016/j.jaac.2021.07.823



PMC full text:
Mov Disord. 2021 Aug 31 : 10.1002/mds.28778.
doi: 10.1002/mds.28778 [Epub ahead of print]

FIG 1

Pringsheim et al (2021) Movement Disorders

New Findings in TS and Inflammatory Processes

Orlovska et al (2017) JAMA Psychiatry

- Investigate link between OCD/tic disorders and infection
- 17y Danish cohort study with >1M youth
- **Strep linked with increased OCD, tics, *any* mental disorder**
- **Non-strep throat infection linked with tics and *any* mental disorder**

Kohler-Forsberg et al (2018) JAMA Psych

- Investigate link between **infections requiring treatment** and risk for mental illness
- Infections (hospitalization):
  - Any mental illness diagnosis - HRR 1.8
  - OCD: 2.7 HRR; **TS: 3.3 HRR**
- Infections (antibiotic):
  - Any mental illness diagnosis - HRR 1.4
  - OCD 2.4 HRR; **TS 3.1 HRR**

New Research Continued

- Mataix-Cols et al (2017) Molecular Psychiatry
  - Swedish birth cohort of 7.5million individuals
  - Individuals with OCD and TS had increased rates of autoimmune disorders (AD) (43% and 36% respectively)
  - Familial link between AD and OCD/TS

- OCD and TS may share genetic risk factors with autoimmune disease
  - Immunological factors may play role in etiology **some** individuals with OCD/CTD

Tsetsos et al (2021) Translational Psychiatry

Perez-Vigil (2016) Neuroscience and

Tourette Syndrome Summary Slide

- Discussed what tics are and how to diagnose Tourette syndrome
- Neuro-circuitry implicated in TS and common associated conditions
- Co-occurring conditions, particularly OCD and ADHD are the rule rather than the exception, and should be treated
- Tics should only be treated if they are causing impairment
  - CBIT is the gold standard behavioral treatment approach
  - Pharmacological treatments can be helpful, but often come with significant adverse effects
  - New medications are in the pipeline
- Increase in observed functional tics, not increase in Tourette syndrome

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