Overview of Pediatric Movement Disorders

David Shprecher, DO Msci
Movement Disorders Director
Banner Sun Health Research Institute

Disclosures

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- Teva (SD-809 for Tourette/HD/TD, pridopidine for HD)
- Neurocrine (Valbenazine for Tourette)
- Kyowa, ADAMAS, NIH, MJFF, Intec, Biotie (Parkinson disease)
- Axovant (Dementia with Lewy bodies)

Personal Biases

- Clinical investigator
- Tics without copralalia

Off label uses will be discussed

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Objectives

1. Identify basic semiology and diagnostic criteria for pediatric movement disorders that are commonly seen in psychiatric practice.
2. Discuss key management considerations for pediatric movement disorders
3. Explain when to consider referral of pediatric movement disorder patients

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Common in Psychiatry

- Primary or Secondary
  - Chorea, Dystonia, Myoclonus, Tremor
  - Tics and Tourette's
  - Stereotypies
- Drug-Induced
  - Tremor
  - Parkinsonism
  - Tardive dyskinesia
- Psychogenic disorders

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Enhanced Physiological Tremor

- Higher Frequency (8-12 Hz)
- Action tremor (Postural and/or kinetic)
- Iatrogenic causes include:
  - Beta-agonists, theophylline
  - SSRIs, TCAs
  - Lithium
  - VPA
  - Cyclosporine, tacrolimus
- Treat w dose reduction or β-blockers

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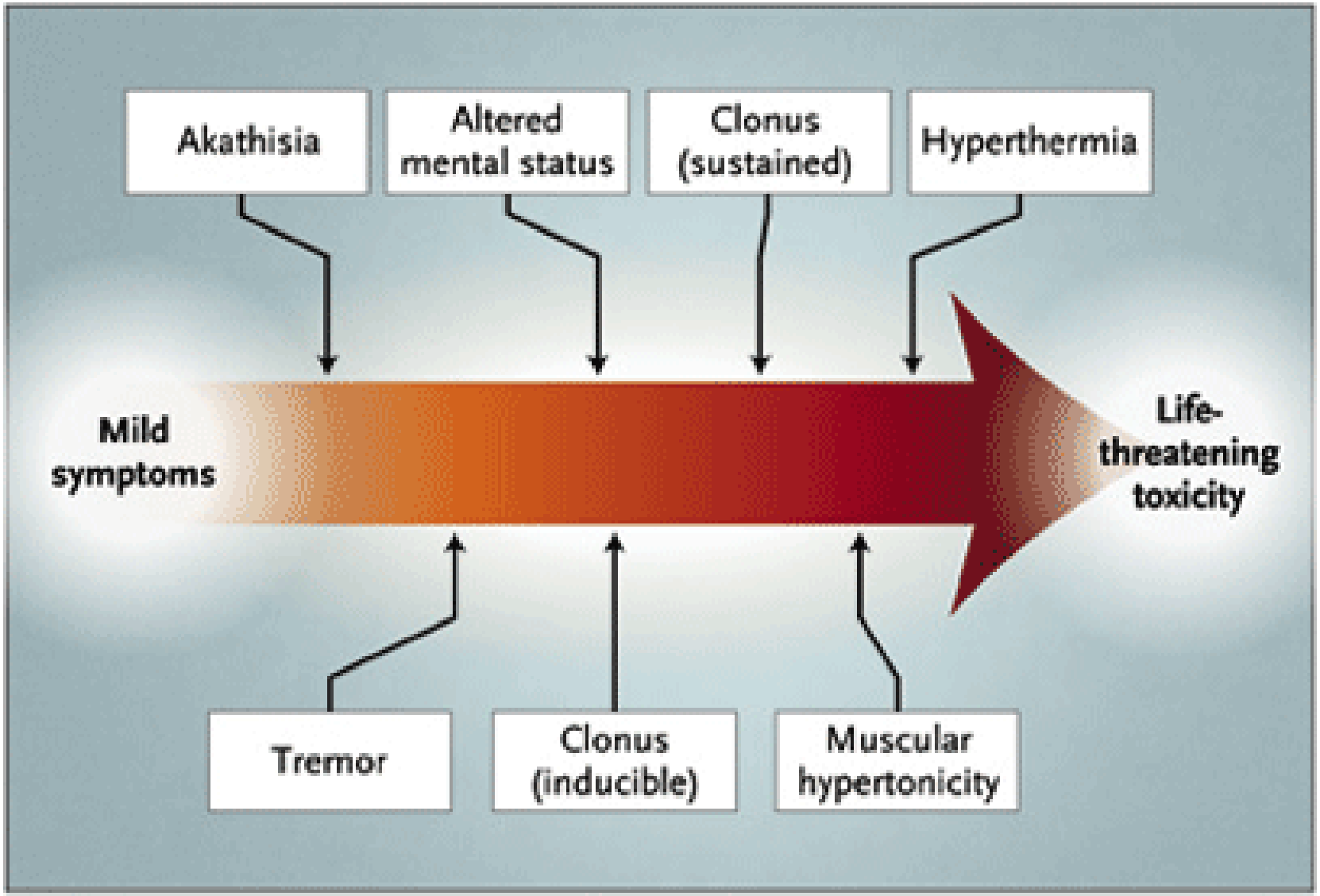
Serotonin Syndrome



Dystonia: definition/etiology

A syndrome of **sustained** muscle contractions, frequently causing **twisting** and repetitive movements or abnormal **postures**.

May be characterized by a sensory trick

- Subtypes
  - Generalized, multifocal, hemidystonia
  - Focal (limb, cranial, cervical)
  - Segmental (craniocervical)
- With AAO<26, consider Genetic Etiologies
  - GTP-CH (Segawa disease)= dopa-responsive
  - DYT1, DYT6

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Tardive Syndromes

- Risk is proportional to dose and duration of agents that reduce D2 receptor activity
  - Antagonist, inverse agonist or partial agonist
- Diagnosis requires prolonged exposure
  - 3 months (1 if age 60+)
- Screen w AIMS (or “modified AIMS”)
  - Assess all body regions, including tongue
  - Assess for emergence with distraction

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DDX: Antipsychotic side effects

- Parkinsonism
- Akathisia
- Withdrawal emergent symptoms
- Tardive Syndromes
  - Stereotypies
  - Dystonia
  - Akathisia
  - Chorea
  - Tics
  - Tremor

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TD Treatment options

- Reduce or D/C APS
- Switch to lower potency agent, clozapine
- Botulinum toxin, DBS
- Off label/limited evidence
  - Amantadine, zonisamide

Rana AQ, Chaudry ZM, Blanchet PJ. New and emerging treatments for symptomatic tardive dyskinesia. Drug Des Devel Ther. 2013 Nov 6;7:1329-40.

Bhidayasiri R, et al. American Academy of Neurology.. Evidence-based guideline: treatment of tardive syndromes: report of the Guideline Development Subcommittee of the American Academy of Neurology. Neurology. 2013 Jul 30;81(5):463-9.

Waln O, Jankovic J. An update on tardive dyskinesia: from phenomenology to treatment. Tremor Other Hyperkinet Mov (N Y). 2013 Jul 12;3.

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Rationale for VMAT-2 inhibitors

- Tetrabenazine Depletes dopamine by blocking presynaptic vesicular storage
- Little risk of tardive dyskinesia, metabolic syndrome
- Post-dose peak contributes to fatigue/somnolence (50%), akathisia, insomnia, depression, anxiety
- Novel approaches can improve area under the curve

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Valbenazine- approved for TD

- Prodrug of the alpha isomer of tetrabenazine
- Slow rate of metabolism to active metabolite allows QD dosing
- FDA approved for TD
  - 40 and 80 mg doses
- SE profile vs placebo
  - Somnolence
    - 5.3 vs 3.9%
  - Akathisia, dry mouth
    - 3.3 v 1.3%

O'Brien et al. NBI-98854, a selective monoamine transport inhibitor for the treatment of tardive dyskinesia: A randomized, double-blind, placebo-controlled study. Mov Disord. 2015 Oct;30(12):1681-7.

Hauser RA, Factor SA, Marder SR, Knesevich MA, Ramirez PM, Jimenez R, Burke J, Liang GS, O'Brien CF. KINECT 3: A Phase 3 Randomized, Double-Blind, Placebo-Controlled Trial of Valbenazine for Tardive Dyskinesia. Am J Psychiatry. 2017 Mar 21

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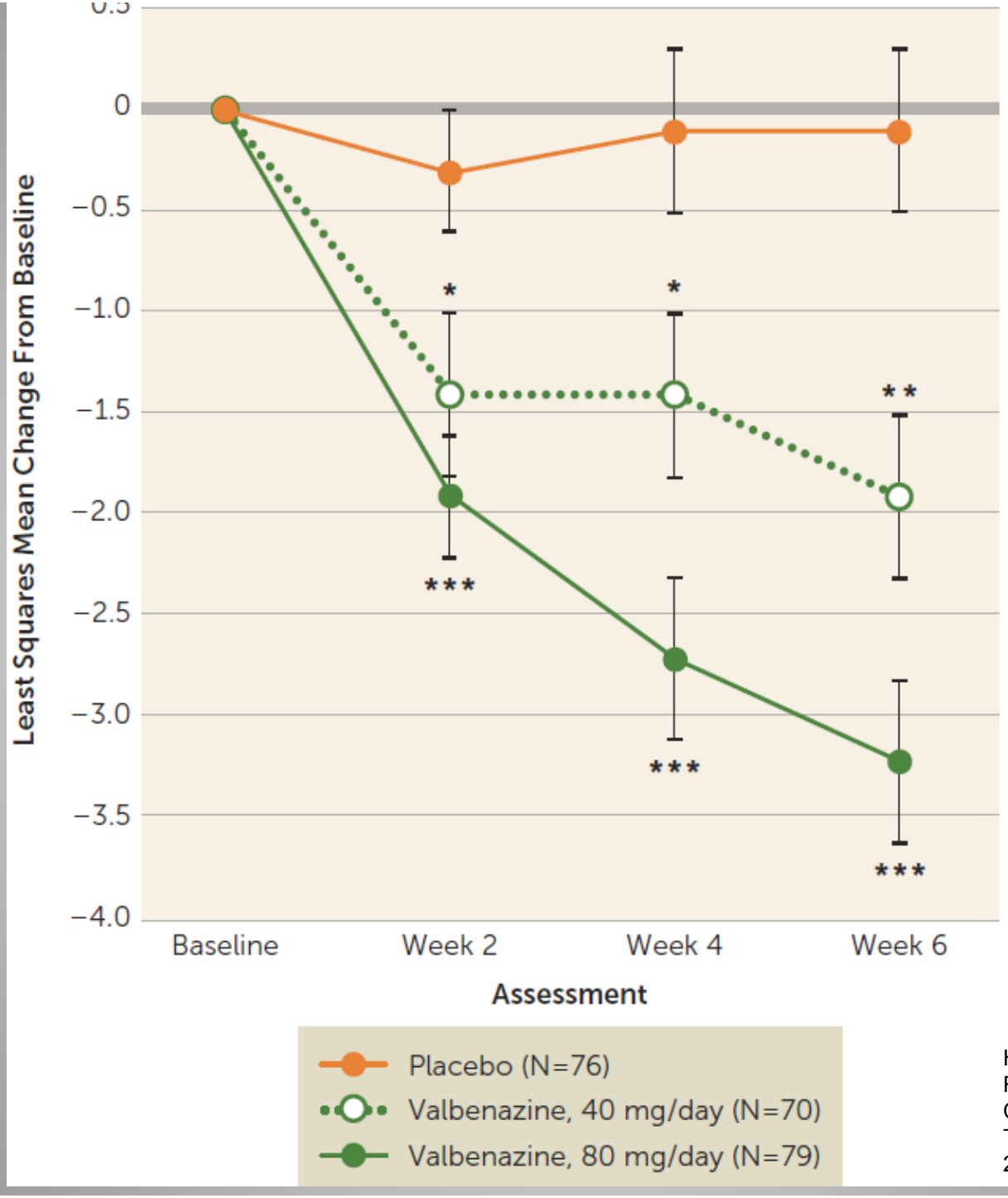
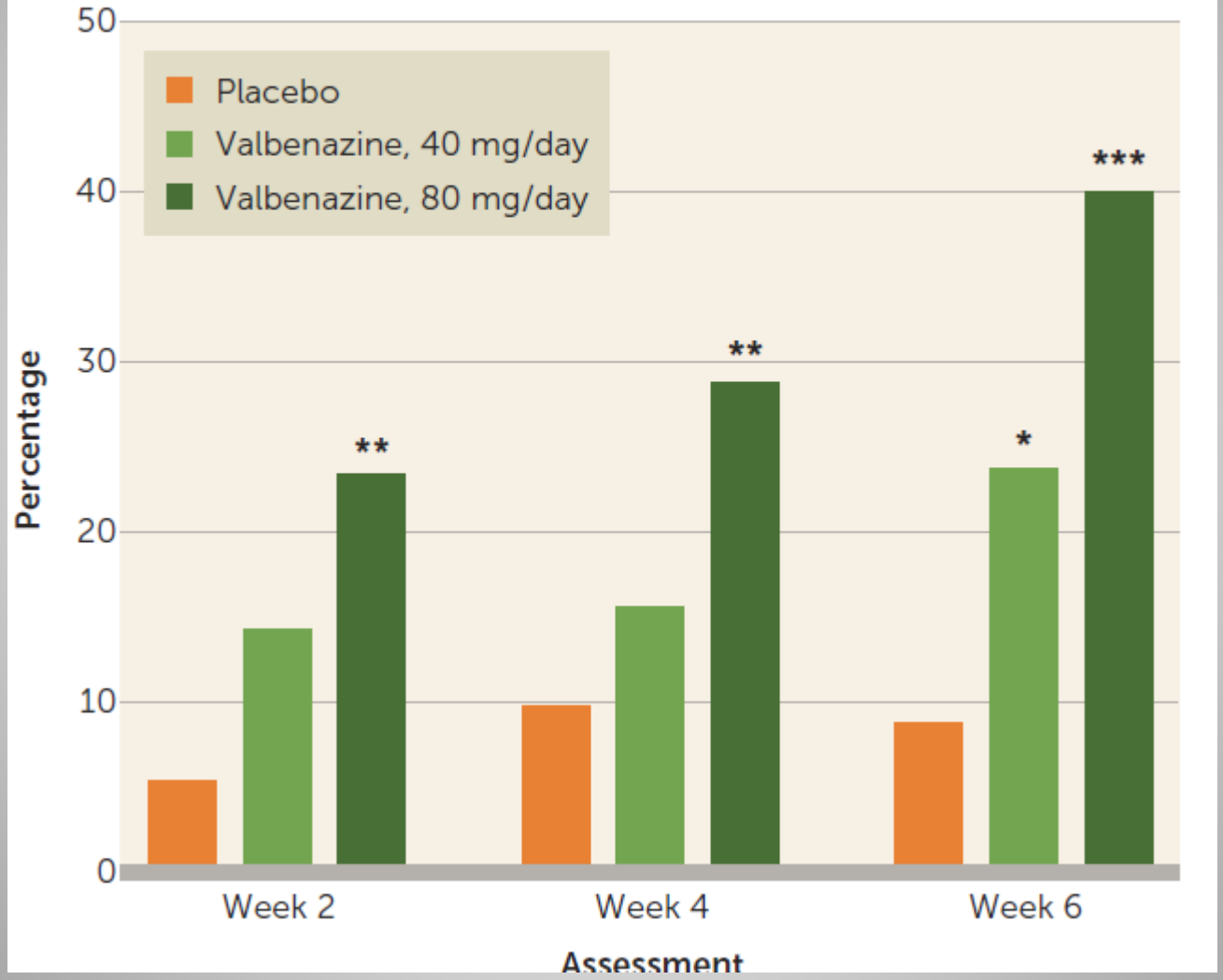


Hauser at al. KINECT 3: A Phase 3 Randomized, Double-Blind, Placebo-Controlled Trial of Valbenazine for Tardive Dyskinesia. Am J Psychiatry. 2017 Mar 21

FIGURE 3. Percentage of Participants Receiving Valbenazine or Placebo Who Had a ≥50% Improvement in AIMS Dyskinesia Score (Intent-to-Treat Population)[a]



Hauser at al. KINECT 3: A Phase 3 Randomized, Double-Blind, Placebo-Controlled Trial of Valbenazine for Tardive Dyskinesia. Am J Psychiatry. 2017 Mar 21

SD-809 (deutetetrabenazine)

- Deuterium slows degradation of active metabolites
- Allows BID dosing
- Approved for HD chorea (24-48mg/d)
- Under review for TD (PDUFA 8/30/2017)
- SE=placebo in TD
- Slightly higher rate of somnolence (11 vs 6%) in HD chorea
- No worsening of mood or parkinsonism

Fernandez HH, Factor SA, Hauser RA, Jimenez-Shahed J, Ondo WG, Jarskog LF, Meltzer HY, Woods SW, Bega D, LeDoux MS, Shprecher DR, Davis C, Davis MD, Stamler D, Anderson KE. Randomized controlled trial of deutetrabenazine for tardive dyskinesia: The ARM-TD study. Neurology. 2017 Apr 26.

Huntington Study Group, Frank et al. Effect of Deutetrabenazine on Chorea Among Patients With Huntington Disease: A Randomized Clinical Trial. JAMA. 2016 Jul 5;316(1):40-50.

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Acute Dystonia

- Prophylaxis: *Short term* treatment with bentropine 2mg/d for one week
  - Reduces risk when using typical antipsychotics
- Causes:
  - DRBs, TCA's, MAOIs, SSRIs, SNRIs,
- Treatment:
  - Withdraw offending agent
  - Treat with antihistamine/anticholinergic

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Stereotypies

- Semi-rhythmic repetitive movement
- Motor
  - Hand rubbing, rocking, prancing
- Vocal
  - humming
- Developmental/degenerative disorders
  - Autistic Spectrum
  - Pervasive developmental delay
  - Rett syndrome
- Tardive

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Tic Characteristics

1. Mimic normal coordinated movement
2. Occur out of a background of normal motor activity
3. Not constantly present
4. Vary in intensity
5. Lack rhythmicity
6. Voluntarily suppressible
7. Usually characterized by a premonitory sensation

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- Tic Video examples (available open access; please go to reference website to stream).

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Key Features Differentiating tics from other hyperkinetic movement disorders

Movement	Stereo-typed	Rhythmic	Premonitory sensations	Suppressible	Continuous	Persist in Sleep
Tic	+	-	+	+	-	+
Myoclonus	+/-	+/-	+/-	-	-	+/-
Dystonia	+/-	-	-	-	+/-	-
Chorea	-	-	-	-	+	-
Sterotypy	+	+	-	+/-	+/-	-
Tremor	+	+	-	-	+/-	-
Psychogenic	+/-	-	+/-	+/-	+/-	+/-

Shprecher D. Tics and Tourette's. Non-Parkinsonian Movement Disorders. Barton B and Hall D. Blackwell Publishing Ltd (In Press)

DSM-V(2013) CRITERIA

307.23 Tourette's Disorder

A. Both multiple motor and one or more vocal tics have been present at some time during the illness, although not necessarily concurrently.

B. The tics occur many times a day (usually in bouts) nearly every day or intermittently throughout a period of more than 1 year
   - (deleted language: "during this period there was never a tic-free period of more than 3 consecutive months.")

C. The onset is before age 18 years.

D. The disturbance is not due to the direct physiological effects of a substance (e.g., stimulants) or a general medical condition (e.g., Huntington's disease or postviral encephalitis).

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Primary Tic Disorders

- Transient tic
- Chronic Motor Tic
- Chronic Phonic Tic
- Tourette syndrome

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Primary Tic Disorders: Prevalence

- Tourette: 1% of boys, 0.25% of girls
- Chronic tic disorder 1.6%
- Transient tic disorder 3%
- Higher overall rates among children requiring special education classes

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When to anticipate a tic?

- Individuals with ADHD, OCD
- Family history of tics, ADHD or OCD
- Special education populations
  - Down syndrome/chromosomal disorders
  - Autistic spectrum/"PDD"
- Unexplained
  - Eye Problems
  - Nose/Throat problems
  - Neck or limb movements due to discomfort
- Pain due to repetitive limb or neck movements

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Comorbidities

- Any psychiatric: 86% (57% 2 or more)
- Obsessive-compulsive disorder 66%
- Attention-deficit/hyperactivity 54%
- Mood 30%
- Anxiety 36%
- Disruptive behavior 29%

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Tics: What to Expect?

- Cleveland Clinic, Yale:
  - 50% “nearly tic free;” 25% same or worse.[1]
- Rush University: 90% “tic free” still have tics[2]
- Utah data (study of ‘tic remission’):[3]
  - 8/10 persistent; 2/10 improved (none tic-free)
- Females outcomes may differ[4]
  - 4.5:1 Juvenile M:F ratio → 2:1 in adult clinics

[1]Erenberg et al, Neurology 1987. [2]Leckman et al, Pediatrics 2000.
[3]Shprecher et al, Tremor and othe
[4]

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Management of Tics

Class	Preferred agents	Special Indications	Common side-effects	Rare or serious AE's
FIRST LINE				
Education	Clinician	Always use	-	-
Nonmedical	CBIT	Motivated	-	-
α-2-agonists	Guanfacine, clonidine	ADHD	Sedation	irritability
Anti-epileptics	Topamax	HA, obesity	hypohydrosis	Kidney stone
SECOND LINE				
Dopamine depletors	tetrabenazine	Tx mood disorder first	Fatigue, depression	Suicide, NMS
Atypical APS	Risperdal, Abilify	Refractory OCD	metabolic	TD, NMS
Typical APS	fluphenazine	Self-injurious tics	EPS	TD, NMS
THIRD LINE				
Surgical-DBS	Thalamic or GPi	Refractory, severe	Infection	Stroke, bleed, psychosis

Shprecher DR, Schrock L, Himle M. Neurobehavioral aspects, pathophysiology, and management of Tourette syndrome. Curr Opin Neurol. 2014 Aug;27(4):484-92.

Comprehensive Behavioral Intervention for Tics (CBIT)

- Education, Removal of reinforcing factors
- Tic (premonitory urge) awareness
- Competing response
- Similar efficacy to medication
  - Pediatric: 31% (vs 14.22% placebo response
  - Adult: 26% (vs 11%)

1: Piacentini et al. Behavior therapy for children with Tourette disorder: a randomized controlled trial. JAMA. 2010 May 19;303(19):1929-37. doi: 10.1001/jama.2010.607.

2: Wilhelm Set al. Randomized trial of behavior therapy for adults with Tourette syndrome. Arch Gen Psychiatry. 2012 Aug;69(8):795-803. doi: 10.1001/archgenpsychiatry.2011.1528.

3: Scahill et al. Current controversies on the role of behavior therapy in Tourette syndrome. Mov Disord. 2013 Aug;28(9):1179-83. doi: 10.1002/mds.25488.

Drugs in Development

Agent	Phase	Sponsor	Mechanism	Main AE's
Acamprosate	II a	Synchroneuron	Glutamate	?
AZD5213	II	Astrazeneca	H3 inv agonist	?
ecopipam	III	Psyadon	D1-R-i	sedation
Sativex	II (?)	GW Pharma	THC/CBD	?
Deu-tetrabenazine	II	Teva	VMAT-2-i	-
Valbenazine	II	Neurocrine	VMAT-2-i	-

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Secondary tic disorders

Etiology	Examples
Autoimmune	Demyelinating disease
Drug-induced	Stimulants, lamotrigine, neuroleptics
Chromosomal disorders	Beckwith Weidemann, Down,or Klinefelter syndromes, Fragile-X
CAG repeat disorders	DRPLA, HD
Genetic mutations	Lesch-Nyhan, Neuroacanthocytosis, NBIA, Wilson, tuberous sclerosis
Infectious (encephalitis)	Mycoplasma, Lyme, syphilis, HSV
Post-infectious	Post-HSV, post-streptococcal
Trama/vascular	TBI, stroke
Toxic	Carbon monoxide

Shprecher, D. Tics and Tourette Syndrome (2017.) In: Non-Parkinsonian Movement Disorders. Barton B, Hall, D eds. Oxford: Wiley-Blackwell.

Stimulant medication- generally considered a comorbidity treatment, not tic cause

- 4x4 Trial- Tourette syndrome study group
  - Methylphenidate, guanfacine
  - Active treatment showed tic improvement
- Methylphenidate (MPH) vs placebo
  - MPH suppressed ADHD, oppositional defiant disorder, and peer aggression behaviors
  - No tic or OCD worsening

1. Tourette's Syndrome Study Group.. Treatment of ADHD in children with tics: a randomized controlled trial. Neurology. 2002 Feb 26;58(4):527-36.
2. Gadow KD, Sverd J, Nolan EE, Sprafkin J, Schneider J. Immediate-release methylphenidate for ADHD in children with comorbid chronic multiple tic disorder. J Am Acad Child Adolesc Psychiatry. 2007 Jul;46(7):840-8.

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Pediatric Autoimmune Disorder Associated with Streptococcal Infection

1. Presence of OCD and/or tics, particularly multiple,complex or unusual tics
2. Age Requirement (Symptoms of the disorder first become evident between 3 years of age and puberty)
3. Acute onset and episodic (relapsing-remitting) course
4. Association with Group A Streptococcal (GAS) infection
5. Association with Neurological Abnormalities, by SC

Swedo SE, Leonard HL, Garvey M, et al. Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections: Clinical description of the first 50 cases. *Am J Psychiatry* 1998;155:264–271.

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PANDAS with chorea= Sydenham's?

- PANDAS-chorea and SC show similar biomarkers
  - Elevated anti-dopamine 1 receptor (D1R) and anti-dopamine 2 receptor (D2R) immunoglobulin (Ig)G levels
  - May cross react with Lysoganglioside-GM1 and tubulin
- PANDAS- chronic tics and OCD (no chorea)
  - Tic/OCD exacerbations did NOT correlate w Strep infection
  - Elevated calcium calmodulin kinase-II activity identified in all 3 groups (SC, PANDAS w/wo chorea)

1. Singer et al. Neuronal antibody biomarkers for Sydenham's chorea identify a new group of children with chronic recurrent episodic acute exacerbations of tic and obsessive compulsive symptoms following a streptococcal infection. PLoS One. 2015 Mar 20;10(3)
2. Leckman et al. Streptococcal upper respiratory tract infections and exacerbations of tic and obsessive-compulsive symptoms: a prospective longitudinal study. J Am Acad Child Adolesc Psychiatry. 2011 Feb;50(2):108-11

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Functional Movement Disorders

- Term preferred over “psychogenic”
- Psychiatric illness may not be comorbid
- If present, etiological life events may require in-depth, specialized interview to identify
- Specialized rehabilitation techniques have been shown beneficial over usual care
- Objective clues about etiology include
  - Loss of sensory attenuation
  - Neuroimaging data: Functional connectivity, fMRI

Pringsheim T and Edwards M. Functional Movement Disorders. Neurology Clinical Practice. April 2017. 141-147

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Factors suggesting a FMD

- Distractibility and/or entrainment (to frequency of repetitive movements)
- False weakness/sensory signs, astasia-abasia
- Inconsistent over time, abrupt onset
- Selective disability
- Co-contraction(tremor)/Bereitschafts(myoclonus)
- Atypical response to pharmacological agent
- Atypical stimulus sensitivity
- Paroxysmal, periods of spontaneous remission

Shill H and Gerber P. Evaluation of Clinical and Diagnostic Criteria for Psychogenic Movement Disorders. Movement Disorders. 21 (8), 2006: 1163-1168.

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Conclusions

- Psychiatric patients should be periodically monitored for movement disorders
- Two new therapies were FDA-approved April 2017 for tardive dyskinesia and chorea.
  - Valbenazine and Deutetrabenazine
  - Modest potential side effects (sedation or fatigue)
  - More research is needed to support on-label treatment of pediatric hyperkinetic movement disorders
- For complex cases, movement disorders neurology consultation is available- and can be considered

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