

ADHD, Tics and Tourette's Disorder Child and Adolescent Psychopharmacology March 21, 2021

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Disclosures (Past 12 Months)

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

- American Academy of Child and Adolescent Psychiatry: Honoraria
- Emalex: Research Support
- HMS /Psychiatry Academy: Honoraria
- NIMH: Research Support
- Partners Healthcare: Honoraria
- Skyland Trail: Advisory Board
- Teva/Nuvelution: Research Support; Scientific Advisory Board
- Tourette Association of America: Co-Chair, Medical Advisory Board; TAA-CDC Partnership

Off label indications will be discussed





"Young man, go to your room and stay there until your cerebral cortex matures."



ADHD, Tics and Tourette's Disorder Learning Objectives

- At the end of this session, the participant should be able to:
- 1) Describe what is known about **boundaries and overlapping** phenomenology of ADHD and tic disorders, including Tourette's Disorder (TD)
- 2) Discuss importance of **disentangling** ADHD and tic symptoms, as this may help guide treatment
- 3) Interpret relevance of these findings for application to treatment of patients with ADHD and tic disorders
- 4) Review strategies for **pharmacological decision making** for youth with ADHD and tic disorders







"I need you to line up by attention span."





ADHD and TD/Tic Disorders: Neurocircuitry

(Leckman, J. et al; JCAP, 2010; 20 (4); 237-247; Robertson, M. Nature Reviews; 2017 (3); 1-20; Malhany, N. et al Eur J Pediatr; 2015; 174; 279-288 <u>)</u>

- Inhibition: core deficit in both disorders; thought to result from fronto-striatal and frontal-parietal network dysfunction in Cortical-Striatal-Thalamic-Cortical (CSTC) tracts.
- **ADHD:** Imaging studies: Reductions in total cerebral volume, PFC, BG, dACC, CC, and cerebellum reported in ADHD patients are consistent with **fronto-striatal models**. Some studies also showed reduction in right cerebral volume, and right caudate nucleus in ADHD.
- **TD:** Mixed results; reduced caudate nucleus volume frequently reported.
- Individuals with TD+ADHD have smaller caudate nuclei.
- **TD+ADHD:** hyper-functioning/overactive circuits in BG in TD result in motor/cognitive/emotional disinhibition, worsened by frontal hypo-activity in ADHD.
- **Both TD and ADHD** tend to improve with time, which may be a result of increased myelinization of prefrontal regions.



Table 3Main brain regions implicated in the pathogenesis of TS andADHD

TS	ADHD	Ref.
+	+	[19, 29, 56]
+	+	[100]
+	+	[19, 29, 55]
+	+	[19, 29, 55]
+	+	[91]
+/	+	[19, 29, 73]
—	+	[29]
	TS + + + + + + -	$\begin{array}{ccc} TS & ADHD \\ + & + \\ + & + \\ + & + \\ + & + \\ + & + \\ + & - & + \\ - & + \end{array}$

(+) implicated region, (-) not implicated region, (+/-) findings contradictory

El Malhany, N. at al. Tourette syndrome and comorbid ADHD: causes and consequences. 2015; Eur J Pediatr 174; 279-288



Table 1 Pre-perinatal risk factors implicated in the pathogenesis of TS and ADHD

Pre-perinatal risk factors	TS	ADHD	Ref.
Alcohol during pregnancy	+	+	[78]
Smoking during pregnancy	+	+	[9, 53]
Prematurity	+	+	[36]
Low birth weight	+	+	[41]

(+) implicated factor

El Malhany, N. at al. Tourette syndrome and comorbid ADHD: causes and consequences. 2015; Eur J Pediatr 174; 279-288



Course of ADHD and Tic Disorders: What Happens to Tics in the Context of ADHD Over Time?

(Spencer, T. Biederman, J. Coffey, B. et al. Arch Gen Psych; 1999, 56: 842-847)

- Design: Prospective ADHD Follow-up
- **<u>Objective</u>**: To evaluate the prevalence and impact of tic disorders at baseline and at follow-up on the course of ADHD.
- <u>Methods</u>: N=128 boys with ADHD; N=110 controls.
- Duration of follow-up: 4 years; mean ages 9-13.
- <u>Results:</u>
 - Proportion of ADHD youth with tics: 34%
 - Remission rate for tics over 4 years: 65%
 - Remission rate for ADHD: 20%
- **<u>Conclusion</u>**: Tic remission rate is independent of ADHD.
- Tic disorders did not impact ADHD course.



Onset of ADHD and Tic Disorders in ADHD Probands (Spencer, T. Biederman, J. Coffey, B. et al. Arch Gen Psych 1999, 56: 842-847)



Offset of ADHD and Tic Disorders in ADHD Probands (Spencer, T. Biederman, J. Coffey, B. et al. Arch Gen Psych 1999, 56: 842-847)



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Chronic Tic Disorders (CTD) in Children with ADHD (Poh, W., Payne, J. et al. Arch Dis Child; 2018; 0; 1-6)

- **Aim:** To examine 1) **prevalence of chronic tics in a community based cohort** in children with ADHD compared to children with non-ADHD at ages 7 and 10
- 2) additional **psychiatric and functional burden of CTD** in children with ADHD. **Methods:** N=179 children age 6-8 with ADHD and 212 healthy controls
- Recruited through 43 schools using parent and teacher Conners followed by case confirmation with DISC-IV.
- Baseline and 36 month follow up evaluations: tic measures; CBCL; academic performance; quality of life.
- **Results:** Compared with controls, children with ADHD were 4 times more likely to have CTD at age 7 and 5.9 times more likely at age 10.
- Concurrent CTD symptoms contribute to higher rates of internalizing disorders, more peer problems and reduced quality of life in children with ADHD.
- **Conclusions:** Clinicians should be aware of and manage both symptoms.



	ADHD+CTD (n=23)	ADHD-only (n=92)	P
ADHD			
Combined subtype, n (%)	7 (30.4)	31 (33.7)	0.79
Inattentive subtype, n (%)	7 (30.4)	30 (32.6)	0.60
Hyperactive/impulsive subtype, n (%)	5 (21.7)	3 (3.3)	0.005
Symptom severity, parent report, mean (SD)	13.7 (5.7)	12.1 (5.5)	0.23
Symptom severity, teacher report, mean (SD)	10 (6.1)	11.0 (6.5)	0.51
Medications			
Medication use (any), n (%)	5 (21.7)	27 (29.3)	0.43
ADHD medication, n (%)	4 (17.4)	16 (17.4)	0.98
ASD symptoms			
SCQ score >15, n (%)	4 (17.4)	7 (7.6)	0.48
Primary caregiver characteristics			
Single parent family, n (%)	4 (17.4)	18 (19.6)	0.49
Did not complete high school, n (%)	7 (30.4)	25 (27.2)	0.83
Completed high school, n (%)	7 (30.4)	26 (28.3)	0.92
Completed higher education, n (%)	6 (26.1)	26 (28.3)	0.75
SEIFA score, mean (SD)	1018.1 (40.3)	1016.6 (46.5)	0.61

ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder; CTD, chronic tic disorder; SCQ, Social Communication Questionnaire; SEIFA, Socio-Economic Indexes for Areas.

Table 2 ADHD+CTD versus ADHD-only—psychiatric outcomes				
	ADHD+CTD (n=23)	ADHD-only (n=92)	Mean difference* (95% CI)	P
Psychiatric outcomes, n (%)				
Internalising disorder	11 (52.4)	20 (23.8)	28.3 (6.1 to 50.6)	0.007
Generalised anxiety disorder	4 (19.1)	3 (3.2)	13.4 (-2.6 to 29.6)	0.03
Separation anxiety disorder	4 (19.1)	9 (10.7)	8.3 (8.5 to 25.1)	0.26
Social anxiety	3 (14.3)	6 (7.1)	5.3 (-9.7 to 20.3)	0.44
Obsessive compulsive disorder	3 (14.3)	7 (8.3)	6.5 (-8.3 to 21.4)	0.31
Post-traumatic stress disorder	0 (0)	0 (0)	-	-
Dysthymia	1 (4.4)	1 (1.1)	3.2 (-5.6 to 11.8)	0.36
Major depression	1 (4.4)	1 (1.1)	3.2 (-5.6 to 11.8)	0.36
Hypomania	0 (0)	0 (0)	-	-
Mania	0 (0)	0 (0)	-	-
Externalising disorder	14 (66.7)	37 (44.0)	11.5 (-11.3 to 34.4)	0.33
Oppositional defiant disorder	14 (66.7)	38 (41.3)	19.6 (-11.3 to 34.4)	0.33
Conduct disorder	3 (13.0)	5 (5.4)	7.6 (-8.3 to 21.3)	0.32

*Difference in mean prevalence (ADHD+CTD minus ADHD). ADHD, attention-deficit/hyperactivity disorder; CTD, chronic tic disorder.



Figure 1. Clinical Hallmarks of Tourette's Syndrome.

The diagnosis is based on the occurrence of tics along with behavioral disorders, including attention-deficit-hyperactivity disorder (ADHD) and obsessive-compulsive disorder (OCD). Other behavioral disorders include anxiety and mood disorders, learning disorders, sleep disorders, conduct and oppositional behavior, and self-injurious behavior.

Jankovic J.NEJM; 2001.

Phenotype Development in Adolescents with Tourette Syndrome: A Large Clinical Longitudinal Study

(Groth, C. Mol Debes, N. et al ; Journal of Child Neurol; 2017; 32 (3) 1047-1057)

Aim: Description of TS phenotype development and tic-related impairment in a longitudinal study of 226 children and adolescents followed up after 6 years.

Methods: Participants examined for tic severity, impairment, OCD and ADHD.

- **Results:** Over time, phenotype development changed toward **less comorbidity**:
- At baseline 40% had TS only (no OCD or ADHD); 55% had TS only at follow up. Tic related impairment scores did not reflect tic decline. Sex, vocal and motor tics, OCD and ADHD severity were highly significantly correlated with tic related impairment score.
- **Conclusion:** Knowledge of phenotype development may be useful in clinical settings.



Table I. Baseline Characteristics of Participants and Nonparticipants at Follow-Up.

Characteristics	Participants	Nonparticipants	P value
Sample size	227	87	_
Age, years, mean(SD)	12.5 (2.7)	12.3 (2.9)	.69
Male, number (%)	185 (81.5)	72 (82.8)	.87
IQ, mean (SD)	90.0 (18.4)	85.3 (16.1)	.07
SES, mean (SD)	2.5 (1.0)	2.7 (1.0)	.10
ADHD, number (%)	93 (41.2)	42 (48.3)	.31
OCD, number (%)	89 (39.2)	33 (37.9)	.90
OCD, CY-BOCS score, mean (SD)	8.4 (8.0)	8.2 (7.9)	.82
Tics YGTSS score, mean (SD)	24.5 (18.2)	25.6 (17.6)	.68

There were no significant differences (P < .05) between any of the demographic variables examined between participants and nonparticipants using Fisher's exact test for sex, SES, ADHD, OCD, and CY-BOCS; and *t*-test for age, tic severity, OCD severity, IQ, and YGTSS.²⁵ Abbreviations: ADHD, attention-deficit/hyperactivity disorder; CY-BOCS, Children's Yale-Brown Obsessive Compulsive Scale; IQ, intelligence quotient; OCD, obsessive compulsive disorder; SES, socioeconomic status; YGTSS, Yale Global Tic Severity Scale.

Journal of Child Neurology 2017, Vol. 32(13) 1047-1057



Figure 1. The development of phenotypes from baseline (T1) to follow-up (T2). At follow-up, the groups were subdivided illustrating the subclinical symptoms into full tic remission (tic score on YGTSS = 0), partial ADHD remission (subthreshold symptoms and impairment according to DSM-IV), inattentive type (ADHD predominantly inattentive type), and subclinical OCD (OCD-score8-9 on Y-BOCS). No participants fulfilled criteria at T2 for ADHD predominantly hyperactive/impulsive type. Abbreviations: ADHD, attention-deficit/hyperactivity disorder; OCD, obsessive compulsive disorder; TS, Tourette syndrome.

Journal of Child Neurology 2017, Vol. 32(13) 1047-1057



"After the lab studies, angiograms, MRI, and the full body CT scans, the physical examination revealed the knife in his back."



Mount Sinai / Presentation Slide / December 5, 2012

Diagnostic Evaluation: Tic Disorders and ADHD: Key Points

- **Diagnoses** of both disorders are made on basis of **classical history.**
- Structured or semi-structured diagnostic interviews, such as the DISC or K-SADS, can improve classification and assessment of comorbidity.
- **Standardized rating scales** have improved diagnostic reliability in research studies; helpful in clinical care.
- The Yale-Global Tic Severity Scale (YGTSS) (Leckman, Riddle, Hardin, Ort, Swartz, Stevenson, et al., 1989); the "gold standard;" assesses domains of: tic number, frequency, intensity, complexity and interference (0-50), and tic related impairment (0-50). Tic Symptom Self Report (TSSR) derived.
- **SNAP, ADHD-RS and Conners** (Parent and Teacher) are helpful for quantitative evaluation of ADHD symptoms.
- Quantitative ratings of tics and ADHD can facilitate 1) disentanglement and 2) prioritization for overall treatment planning and 3) use of targeted combined pharmacotherapy.



TD/Tics and ADHD: Management Strategies

- **Tics:** Most patients with mild tic symptoms need only monitoring, education, and guidance. Those with moderate to severe symptoms will usually need treatment.
- ***ADHD: Since ADHD symptoms are more likely to persist and cause significant functional impairment, treatment is recommended.
- **Comprehensive Behavioral Intervention for Tics (CBIT)** is established as **first line treatment** for tics. This may be particularly relevant to patients with tics and ADHD, since pharmacotherapy may be challenging. ADHD did not moderate response to CBIT. *(Sukholdosky, D. et al, Neurology, 2017)*
- Pharmacotherapy for Tic Disorders and ADHD:
- 1) stimulants
- 2) alpha agonists
- 3) atomoxetine
- 4) combinations



Modified CBIT study (MCBIT) Erica Greenberg MD and Team

Modified Comprehensive Behavioral Intervention for Tics: Treating Children with Tic Disorders, Cooccurring ADHD and Psychosocial Impairment

- Develop a manual that modifies current treatment by combining CBIT with CBT for ADHD and other CBT techniques that target psychosocial consequences of tic disorders
- Conduct a small pilot study randomizing youth with tic disorders and ADHD to standard CBIT group or modified CBIT group



Meta Analysis: Risk of Tics Associated with Stimulant Use in Randomized, Placebo-Controlled Trials

(Cohen, S. Mulqueen, J. Ferracioli-Oda, E. Stuckelman, Z. Coughlin, C, Leckman, J. Bloch, M. JAACAP; 2015; 54(9); 728-736)

- **Design**: Meta-analysis of RCTs of stimulants in treatment of ADHD.
- **<u>Results</u>**: N=22 studies with 2385 children with ADHD.
- New onset or worsening of tics were commonly reported with *stimulants (5.7%) and placebo groups (6.5%)*.
- Risk of new onset or tic worsening associated with stimulants was similar to that of placebo (risk ratio=0.99, p=.962).
- **<u>Results:</u>** Stimulant type, dose, duration and age did not affect risk.
- Cross over studies were associated with a significantly greater risk than parallel group trials.
- <u>Conclusion</u>: There is **no evidence** for support of an association between new onset or worsening of tics with stimulant use in patients with



Practical Tips on Treating ADHD and Tics/TD with Stimulants

- When ADHD is the more problematic disorder, a stimulant is first line treatment. Of the two classes, a methylphenidate (MPH) is recommended.
- For children, MPH can be initiated at 5 mg (or equivalent) and titrated upward gradually.
- For adolescents, MPH can be initiated at 10 mg (or equivalent) and titrated upward gradually.
- It can be helpful to start with an immediate release (IR) preparation, and then once an effective and tolerable dose is reached, switch to a long acting delivery system.



Practical Tips on Treating ADHD and Tics/TD with Stimulants

- There are no controlled trials of **extended release stimulants**, but they may be less likely than IR to be associated with tic increase that occurs in some children.
- For tic increase/exacerbation with upward titration: if ADHD symptoms have improved, hold the dose and monitor, or temporarily reduce the dose and re-titrate.
- Guanfacine or clonidine can be added if the tic increase is sustained.
- If the A2A plus stimulant is not optimal for management of both ADHD and tics, a switch to atomoxetine is recommended.





PSYCHIATRY ACADEMY

Atomoxetine Treatment of ADHD in Children with Comorbid Tourette syndrome (Spencer, T. et al. J. Attn Disord; 2008; 11 (4); 470-481)

- **Method:** Subjects (7-17) with ADHD (DSM-IV) and TS randomly assigned to double-blind treatment with placebo (n = 56) or ATMX (0.5-1.5 mg/kg/day, n = 61) for approximately 18 weeks.
- **Results:** ATMX subjects showed significantly greater improvement on ADHD symptom measures than placebo.
- Treatment was also associated with significantly greater reduction of tic severity on two of three measures.
- Adverse effects: Significant increases in mean pulse rate, and nausea, reduced appetite, and decreased body weight.
- No other clinically relevant treatment differences were observed in any other vital sign, adverse event, laboratory parameter, or electrocardiographic measure.
- **Conclusion:** ATMX is efficacious for treatment of ADHD, and its use appears well tolerated in ADHD patients with comorbid TS.



Atomoxetine Treatment of ADHD in Children with Comorbid Tourette syndrome

(Spencer, T. et al. J. Attn Disord; 2008; 11 (4); 470-481)

Figure 1

Changes from Baseline Over Time in Least-Square Mean (LS Mean) Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator-administered and -scored (ADHDRS-IV-Parent:Inv) Total Scores, Mixed-Model Repeated Measures Analysis



Note: Atomoxetine group (0.5-1.5 mg/kg/day, b.i.d.; n = 60; filled circles/solid line) relative to placebo group (n = 56; open circles/ dashed line). *p = .017. **p = .002.

How To Decide? Systematic Review: Pharmacological Treatment of Tic Disorders: Efficacy of Antipsychotic and Alpha 2 Agonist Agents

(Weisman, H. Qureshi, I. Leckman, J. Scahill, L. Bloch, M. Neuroscience and Biobehavioral Reviews; 2013; 37; 1162-1171)

- **Design**: Meta-analysis of RCTs in treatment of chronic tic disorders and examination of moderators
- **<u>Results</u>**: Significant benefit of antipsychotics vs. placebo. **SMD=0.58**.
- No significant difference in efficacy of risperidone, pimozide, haloperidol and ziprasidone.
- Significant benefit of alpha 2 agonists vs. placebo. Significant moderating effect of comorbid ADHD.
- With comorbid ADHD SMD: 0.68. No ADHD: 0.15.
- <u>**Conclusion**</u>: Significant benefits of both medication types, but alpha 2 agonists may have minimal benefit in patients without ADHD.





Percent of Sample with ADHD

Fig. 7. (A) Efficacy of alpha2-agonists for the treatment of tics in trials stratified by ADHD comorbidity. Trials that required tic patients to have comorbid ADHD (SMD=0.68 (95%CI: 0.36-1.01), z=4.10, p<0.001) demonstrated a significantly greater effect (test for subgroup differences χ^2 =7.27, df=1, p=0.007) of alpha-2 agonists in reducing tic symptoms than trials that excluded subjects with comorbid ADHD (SMD=0.15 (95%CI: -0.06 to 0.36), z=1.40, p=0.16). (B) Meta-regression of alpha-2 agonist efficacy in treating tics versus percent of subjects with comorbid ADHD in trial. Meta-regression demonstrated that trials enrolling a larger proportion of subjects with comorbid ADHD reported a greater efficacy of alpha-2 agonists in treating tics (β =0.0053 (95%CI: 0.0015-0.0091), z=-2.72, p=0.006).



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"I'm not going to shoot the messenger, but I'm also not going to renew his grant."

TUESDAY

Canada Day

Extended-Release Guanfacine (GXR) Does Not Show a Large Effect on Tic Severity in Children with Chronic Tic Disorders

(Murphy T, Fernandez T, Coffey B, et al. JCAP. 2017;27(9):762–770.)

- Methods: 8-week RCT in N=34 youth ages 6 to 17 years (mean = 11.1) with CTD.
- Results: At baseline, mean YGTSS total score was 26.3 for GXR group vs.
 27.7 for placebo.
- GXR group: (mean final daily dose 2.6 mg.); mean YGTSS total score declined to 23; p = 0.08; effect size = 0.35.
- PBO group: declined to 24.7; **p = 0.08; effect size = 0.38.**
- There was no significant difference in the rate of positive response on CGI-I between GXR and PBO (19% vs. 22%; p = 1.0).
- Adverse Effects (AE): Most common: fatigue, drowsiness, dry mouth, headache, and irritability.
- **Conclusion:** This pilot study **did not confirm a clinically meaningful effect size** within GXR group. These results **do not support launch** of a larger efficacy trial for tics in youth with CTD.

Extended-Release Guanfacine (GXR) Does Not Show a Large Effect on Tic Severity in Children with Chronic Tic Disorders (Murphy T, Fernandez T, Coffey B, et al. JCAP. 2017;27(9):762–770.)



FIG. 2. YGTSS total score, motor, and phonic; guanfacine vs. placebo. YGTSS, Yale Global Tic Severity Scale.

Implications for Practice: (Cochran Review; 2018) Pharmacological Treatment for ADHD in Children with Comorbid Tic Disorders (Osland ST, Steeves TDL, Pringsheim T)

- **Stimulants** have generally been thought to provide the most reliable and robust treatment responses for symptoms of ADHD in children with tics.
- Given methodological difficulties in comparing ES across studies with divergent inclusion criteria, efficacy measures, and designs, this review can provide no evidence-based recommendations for choosing between treatment options.
- Stimulants will likely continue to be considered as first-line treatment for children with moderate to-severe symptoms of ADHD in children with tic disorders.
- Although overall, stimulants have not been shown to worsen tics in most participants with tic disorders, they may still exacerbate tics in individual cases.
- In these instances, treatment with **alpha agonists or atomoxetine** could be considered as alternatives.







"If you're happy and you know it, stick with your dosage."

SEPTEMBER 25



Summary: ADHD, Tics and Tourette's Disorder

- There is **bi-directional overlap of ADHD and Tic Disorders.**
- ADHD symptoms tend to persist, but tic symptoms tend to remit over time.
- Much of the **associated psychopathology (behavioral, emotional, neurocognitive**) in Tourette's Disorder is secondary to ADHD.
- **Outcomes** are generally less favorable for ADHD than tic disorders.
- Children and adults with **ADHD+CTD** are more likely to have higher rates and severity of psychopathology and reduced quality of life than those with either ADHD or CTD alone.
- Tic and ADHD symptoms should be carefully **disentangled**, by severity and potential outcomes, for best management and intervention.
- **Stimulants** can be used safely for treatment of ADHD and tics, as ADHD is typically the more problematic of the two.
- There are several other options, including atomoxetine, and combination treatment with alpha 2 agonists.



Acknowledgements:

Jill Ehrenreich-May, Ph.D. Co-Director, University of Miami Miller School of Medicine TAA Center of Excellence

Vilma Gabbay, M.D. M.S Associate Professor, Department of Psychiatry, Icahn SOM at Mount Sinai

Joseph Jankovic, M.D. Professor of Neurology Baylor College of Medicine

Betsy Garafalo, M.D. Nuvelution

Mark Gordon, M.D. Teva Pharmaceuticals

Maria Cruz, B.A. Research and Clinical Coordinator, UM Miller School of Medicine

Cynthia Fundora, B.A Research Coordinator, UM Miller School of Medicine.