Tourette’s and Tic Disorders, ADHD and Comorbidity
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# Disclosures of Potential Conflicts

<table>
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<tr>
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<th>Advisor Consult</th>
<th>Employee</th>
<th>Speakers Bureau</th>
<th>Books, Intellectual Property</th>
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</tbody>
</table>
“Young man, go to your room and stay there until your cerebral cortex matures.”
“I need you to line up by attention span.”
Tourette’s and Tic Disorders, ADHD and Comorbidity

Learning Objectives

• To review:
  • Bidirectional overlap between ADHD and tic disorders
  • Prevalence and impact of tic disorders in ADHD in clinically referred youth and adults
  • Update on relevant research on ADHD and tic disorders
  • Update regarding use of stimulants in comorbid ADHD and tic disorders
  • Guidelines for pharmacological treatment of comorbid ADHD and tic disorders
Epidemiology: Bi-Directional Overlap of ADHD and Tic Disorders

• 1) Rates of tic disorders are higher (10-30%) in children with Attention Deficit Hyperactivity Disorder (ADHD) than in children without ADHD (1-10%) (Spencer, Biederman, Coffey et al., Arch Gen Psych; 1999, 56: 842-84)

• 2) Rates of comorbid ADHD are high (50-75%) in clinically referred children with Tourette’s Disorder (TD). (Coffey, Biederman, Spencer et al. J Nerv Ment Dis; 2000; 188:583-588; Freeman, Tourette Syndrome International Data base Consortium; Eur Child Adolesc Psych 2007; 16 [suppl; 1];1/15-1/23)

• 3) Rates of ADHD in a community sample of TD were higher (8.3%) than ADHD population prevalence (3.9%) (Apter et al, 1993)
Classification: DSM-IV-TR 2000 Tic Disorders

DSM V: Neurodevelopmental Disorders: Motor Disorders

- **Transient tic disorder**: one or more tics present for greater than 4 weeks, but less than 12 months
- **Provisional tic disorder**: Single or multiple motor tics and/or vocal tics; present for less than 1 year since first tic onset. Onset before age 18.
- **Chronic motor or vocal tic disorder**: one or more motor or vocal tics present for greater than 1 year
- **Tourette’s Disorder**: Both multiple motor and one or more vocal tics have been present at some time during the illness, although not necessarily concurrently. Tics occur many times a day (usually in bouts), nearly every day or intermittently throughout a period of more than 1 year, and during this period there was never a tic-free period of more than 3 consecutive months. Onset before 18 years.
  - The tics may wax and wane in frequency but have persisted for more than a year since first tic onset.
  - **Tic Disorder NOS**
  - **Unspecified Tic Disorder**
Inhibition is a core deficit in both disorders

Executive functions abnormalities in both thought to result from fronto-striatal and frontal-parietal network dysfunction

**ADHD**: In youth, smaller volumes in DLPC, caudate, pallidum, corpus callosum and cerebellum (Seidman et al; 2005)

**ADHD**: Across studies, significant patterns of frontal hypoactivity in ADHD, including ACC, DLPC, inferior prefrontal, and related regions: basal ganglia, thalamus and parietal cortex.

**TD**: Approximate 5% reduction in caudate volume reported in both children and adults with TD (Peterson et al; 2003).

Inverse correlation between caudate volume in childhood and tic severity in early adulthood (Bloch et al; 2005)

Cortical thinning in youth reported in sensory and motor areas, correlating with worst ever tic severity (Sowell et al; 2008).

**TD+ ADHD**: CTSC misguided neural oscillations may result in BG disinhibition, worsened by frontal hypoactivity in ADHD. Since both TD and ADHD improve with time, may be due to increased myelinization of prefrontal regions.
Tourette’s Disorder: Natural History: Does it Remit or Persist?


• Course: “……..The duration of the disorder is usually lifelong, though periods of remission lasting from weeks to years may occur………..”

Tic severity:

• Research in the past decade suggests peak severity occurs at about age 10-11 years with improvement into adolescence (retrospective birth cohort design)

Time Course of Tic Severity Ratings

Tic Disorders: Administrative Prevalence and Co-occurrence with ADHD in a German Community Sample (Schlander et al. European Psychiatry; 26 (2011); 370-374)

ADHD: 5%. Tic disorders in 2.3% of ADHD patients.
Informativeness of Structured Diagnostic Interviews in the Identification of Tourette’s Disorder in Referred Youth

(Coffey, B. et al. J. Nerv. Ment. Dis. 2000; Sep; 188 (9): 583-588)

Clinical and Demographic Characteristics of Non-specialized and Specialized Clinic Patients with TD

<table>
<thead>
<tr>
<th></th>
<th>Non-specialized Clinic patients (N=92)</th>
<th>Specialized Clinic patients (N=103)</th>
<th>Overall Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
</tr>
<tr>
<td>Current Age</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>10.8</td>
<td>3.23</td>
<td>10.8</td>
</tr>
<tr>
<td>SES</td>
<td>2.0</td>
<td>1.13</td>
<td>2.2</td>
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<tr>
<td>Past GAS</td>
<td>47.9</td>
<td>7.50</td>
<td>48.6</td>
</tr>
<tr>
<td>Current GAS</td>
<td>51.3</td>
<td>7.32</td>
<td>51.9</td>
</tr>
<tr>
<td>% Male</td>
<td>82</td>
<td>90</td>
<td>81</td>
</tr>
</tbody>
</table>
## Comorbidity: Disruptive Behavior Disorders

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Non-specialized Clinic Patients (N = 92)</th>
<th>Specialized Clinic Patients (N = 103)</th>
<th>Overall Significance</th>
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<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>ADHD</td>
<td>76</td>
<td>84</td>
<td>74</td>
</tr>
<tr>
<td>Conduct Disorder</td>
<td>18</td>
<td>20</td>
<td>14</td>
</tr>
<tr>
<td>Oppositional Defiant Disorder</td>
<td>63</td>
<td>69</td>
<td>58</td>
</tr>
<tr>
<td>Any Disruptive Disorder</td>
<td>83</td>
<td>91</td>
<td>86</td>
</tr>
<tr>
<td>*Pure TD (Non-comorbid)</td>
<td>2</td>
<td>2</td>
<td>5</td>
</tr>
</tbody>
</table>
Comprehensive assessment of clinically referred youth with Tourette’s Disorder is essential.

Irrespective of ascertainment site, children meeting diagnostic criteria for TD on SDI share similarities and patterns of clinical correlates.

Findings may generalize to other clinical settings.

SDIs are useful tools in identification of TD.

(Coffey B, Biederman J, Spencer T, Geller D, Faraone S, Bellordre C. J Nerv Ment Dis. 2000; Sep;188 (9):583-588)
Course of ADHD and Tic Disorders: What Happens to Tics in the Context of ADHD Over Time?

- **Design**: Prospective ADHD follow-up
- **Objective**: To evaluate the prevalence and impact of tic disorders at baseline and at follow-up on the course of ADHD.
- **Methods**: N=128 boys with ADHD; N=110 controls
- **Duration of follow-up**: 4 years.

(Spencer, Biederman, Coffey, et al. Arch Gen Psych 1999, 56: 842-847)
Rates of Tic Disorders in ADHD & Control Probands

ADHD Controls
Baseline

ADHD Controls
Follow-up

ADHD Controls
Overall
Onset of ADHD and Tic Disorders in ADHD Probands

- ADHD
- Tic Disorders

Age in Years

%
Offset of ADHD and Tic Disorders in ADHD Probands

- ADHD
- Tic Disorders

Age in Years: 0, 5, 10, 15, 20, 25

%: 100, 90, 80, 70, 60, 50, 40, 30, 20, 10, 0

Graph showing the percentage of ADHD and Tic Disorders over age in years.
Course of ADHD and Tic Disorders

• **Results:**
  • Proportion of ADHD youth with tics: 34%
  • Remission rate for tics over 4 years: 65%
  • Remission rate for ADHD: 20%

• **Conclusion:** Tic remission rate is independent of ADHD

• Tic disorders did not impact ADHD course

• *(Spencer, Biederman, Coffey, et al. Arch Gen Psych 1999, 56: 842-847)*
You will like Mr. Woofard. He has an attention-deficit disorder.
Impact of Tic Disorders on ADHD Outcome Across the Life Cycle: Findings from a Large Group of Adults With and Without ADHD


- **Objective:** To assess impact of presence of tic disorder on the course of ADHD in adults.
- **Methods:** Blinded, retrospective assessment by Structured Clinical Interview for DSM IV (SCID), supplemented with modules from the K-SADS-E covering childhood diagnoses.
- **N=**312 adults with ADHD; **N=**252 adult controls
- **Results:** Significantly greater proportion of adults with ADHD (12%) than those without ADHD (4%) had tic disorders
- Tic disorders followed mostly a remitting course and had little impact on functional capacities.
- **Conclusion:** Adult findings confirm and extend previous findings in youth with ADHD, documenting that although individuals with ADHD are at greater risk for tic disorders, the presence of tics has limited impact on ADHD outcome.
Developmental Course of Tourette’s Disorder and ADHD

Developmental Psychopathology of Children and Adolescents with Tourette Syndrome-Impact of ADHD
(Roessner et al. Eur Child Adolesc Psych; 2007; 16;1/24-1/25)

Design and Subjects: N=5060 patients in 67 tertiary centers in 27 countries: TS International Data Base Consortium. Cross-sectional design; youth age 5-17 years

Findings:
1. Higher rate of comorbidity in TD+ADHD than TD-ADHD in children and adolescents
2. Rate of OCD was higher in TD+ADHD in children (age 5-10) but not adolescents (age 11-17). But OCD developed more rapidly year to year in the TD-ADHD group
Year-wise changes of the rate of comorbidities in children and adolescents with TD versus TD+ADHD in (a) number of comorbidities and (b) obsessive compulsive disorder.

Roessner, Eur Child Adolesc Psychiatry, 2007
Developmental Course of Tourette’s Disorder and ADHD (Roessner et al. Eur Child Adolesc Psych; 2007; 16;1/24-1/25)

N=5060 patients in 67 tertiary centers in 27 countries: TS International Data Base Consortium. Cross-sectional; youth age 5-17 years

1. Rate of comorbid ODD/CD was higher in youth with TD+ ADHD than TD-ADHD
2. Mood disorders were more frequent in children with TD+ ADHD, but the rate of increase was independent of ADHD
3. Anxiety disorders were slightly more frequent in TD+ ADHD in children, but not in adolescents; rate of anxiety disorders rose more rapidly in TD-ADHD
Year-wise changes of the rate of comorbidities in children and adolescents with TD versus TD+ADHD in (c) anxiety disorders, (d) conduct disorders/oppositional defiant disorder, (e) mood disorders.

Roessner, Eur Child Adolesc Psychiatry, 2007


Neuropsychological Functioning in Children with Tourette Syndrome with and without Attention Deficit Hyperactivity Disorder (Sukhodolsky, D. Landeros-Weisenberger, A. Scahill L., Leckman, J. Schultz, R. JAACAP, Vol. 49 (11), November 2010; 1155-1164)

- **Aim**: Compare neuropsychological tests in children with TD, TD+ADHD, ADHD, and healthy controls
- **Design**: N=56 TD, 45 TD+ADHD, 64 ADHD, 71 HC
- **Tests**: CPT, Stroop, Beery VMI, Purdue Pegboard
- **Results**: TD children did not differ from HC on measures of response inhibition and VMI.
- ADHD children were impaired on all study measures.
- Boys with TD, but not girls, were impaired in dominant hand Purdue performance.
- TD+ADHD had no deficits on Stroop, VMI, and Purdue, but were impaired on sustained attention of CPT.
- **Conclusion**: Comorbid ADHD is associated with neuropsychological deficits in children with TD.
Neuropsychological Performance of Children with TD, Children with TD+ADHD, Children with ADHD, and Unaffected Controls

<table>
<thead>
<tr>
<th></th>
<th>TS</th>
<th>TS+ADHD</th>
<th>ADHD</th>
<th>Controls</th>
<th>Analysis</th>
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<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
</tr>
<tr>
<td>Conners’ CPT</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Errors of omission (%)</td>
<td>4.55</td>
<td>3.70</td>
<td>6.78</td>
<td>6.28</td>
<td>5.79</td>
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<tr>
<td>Errors of commission [%]</td>
<td>53.35</td>
<td>22.65</td>
<td>55.90</td>
<td>22.46</td>
<td>58.38</td>
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<td>Reaction time (ms)</td>
<td>414.55</td>
<td>76.61</td>
<td>423.12</td>
<td>88.45</td>
<td>429.50</td>
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<td>RT variability (SE)</td>
<td>11.76</td>
<td>5.90</td>
<td>13.81</td>
<td>6.50</td>
<td>15.02</td>
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<tr>
<td>Stroop</td>
<td></td>
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<tr>
<td>Golden Interference Score</td>
<td>168.57</td>
<td>77.25</td>
<td>171.63</td>
<td>75.57</td>
<td>180.41</td>
</tr>
<tr>
<td>Purdue</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Dominant raw score²</td>
<td>13.55</td>
<td>2.21</td>
<td>13.47</td>
<td>1.90</td>
<td>13.10</td>
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<tr>
<td>Nondominant raw score</td>
<td>12.53</td>
<td>1.89</td>
<td>12.64</td>
<td>1.97</td>
<td>12.19</td>
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<tr>
<td>Bimanual raw score</td>
<td>10.35</td>
<td>1.69</td>
<td>10.37</td>
<td>1.75</td>
<td>10.09</td>
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<tr>
<td>WMI</td>
<td>100.44</td>
<td>15.59</td>
<td>92.89</td>
<td>14.26</td>
<td>88.65</td>
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</table>

Note: CPT = Continuous Performance Test; NC = normal controls; RT = reaction time; SE = standard error; WMI = Beery Visual Motor Integration Test.

Significant main effect of gender interaction effect: $F_{(1,120)} = 4.12$, $p < .05$. Revealed that boys but not girls with TS only were impaired in their dominant hand Purdue performance.

Sukhodolsky, JAACAP, 2010
Psychosocial Outcome and Psychiatric Comorbidity in Older Adolescents with Tourette Syndrome
(Gorman, D. Thompson, N. Plessen, K. Robertson, M. Leckman, J. and Peterson, B.; Br J Psych; 2010; 197; 36-44)

• **Aim**: To compare psychosocial outcome and lifetime comorbidity rates in older adolescents with TD and controls

• **Design**: N=65 with TD identified in childhood, and 65 matched community controls, assessed at age 18

• **Results**: Compared with controls, TD individuals had substantially lower CGAS scores and higher rates of ADHD, MDD, and CD (p <0.01). In those with TD, poorer psychosocial outcomes were associated with greater ADHD, OCD and tic severity.

• **Conclusion**: Clinically referred youth with TD have impaired psychosocial outcome and high comorbidity rates in late adolescence.
Comparison of lifetime psychiatric disorders in the Tourette syndrome group and community controls

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Tourette Syndrome (n = 65)</th>
<th>Controls (n = 65)</th>
<th>Test statistic</th>
<th>Conditional logistic regression</th>
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<tbody>
<tr>
<td>Any psychiatric disorder (including OCD)</td>
<td>61 (93.8)</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Any psychiatric disorder except OCD</td>
<td>60 (92.3)</td>
<td>37 (56.9)</td>
<td>21.5</td>
<td>21.5 (2.9–161.1) &lt; 0.01</td>
</tr>
<tr>
<td>ADHD</td>
<td>43 (66.2)</td>
<td>9 (13.8)</td>
<td>37.1</td>
<td>7.3 (2.8–19.5) 10⁻⁴</td>
</tr>
<tr>
<td>OCD</td>
<td>25 (38.5)</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Anxiety disorder (non-OCD)</td>
<td>26 (40.0)</td>
<td>16 (24.6)</td>
<td>3.5</td>
<td>2.0 (0.8–4.8) 0.1</td>
</tr>
<tr>
<td>Learning disorder</td>
<td>27 (41.5)</td>
<td>8 (12.3)</td>
<td>14.1</td>
<td>7.9 (2.2–28.2) 0.001</td>
</tr>
<tr>
<td>Stuttering</td>
<td>8 (12.3)</td>
<td>5 (7.7)</td>
<td>0.8</td>
<td>2.2 (0.5–9.7) 0.3</td>
</tr>
<tr>
<td>Conduct disorder</td>
<td>15 (23.1)</td>
<td>2 (3.1)</td>
<td>11.4</td>
<td>7.8 (1.7–36.8) 0.01</td>
</tr>
<tr>
<td>Major depressive disorder</td>
<td>40 (61.5)</td>
<td>17 (26.2)</td>
<td>16.5</td>
<td>4.2 (1.8–9.7) 0.001</td>
</tr>
<tr>
<td>Dysthmic disorder</td>
<td>7 (10.8)</td>
<td>3 (4.6)</td>
<td>1.7</td>
<td>3.8 (0.9–16.7) 0.08</td>
</tr>
<tr>
<td>Bipolar disorder</td>
<td>4 (6.2)</td>
<td>0 (0.0)</td>
<td>2.3</td>
<td>1 (0.08–1.1) 0.2</td>
</tr>
<tr>
<td>Primary psychotic disorder</td>
<td>8 (7.7)</td>
<td>0 (0.0)</td>
<td>3.3</td>
<td>0.07</td>
</tr>
<tr>
<td>Substance use disorder</td>
<td>9 (13.8)</td>
<td>6 (9.2)</td>
<td>0.7</td>
<td>1.7 (0.5–6.1) 0.4</td>
</tr>
</tbody>
</table>

Gorman, BJ Psych, 2010
ADHD/TD/Tics: Diagnostic Evaluation

- **Structured diagnostic interviews**, such as the Children's Schedule for Affective Disorders and Schizophrenia (K-SADS) can improve classification and the 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) is considered “gold standard.” The YGTSS assesses domains of tic number, frequency, intensity, complexity and interference (0-50), and tic related impairment (0-50).
“These medicines all taste pretty good—let’s approve them.”
“Ask your mother if this medicine is right for you.”
ADHD/TD/Tics: Overview of Treatment

**Pharmacotherapy** is cornerstone.

**Tics:** Most patients with mild tic symptoms need only monitoring, education, and guidance.

Given converging evidence that tics peak in severity before early adolescence, it may be most judicious to “wait it out” with **support and monitoring** through this developmental phase.

**ADHD:** Since ADHD symptoms are more likely to persist and cause significant functional impairment, treatment is usually mandatory.
**Effectiveness Categories of Tic-Suppressing Medications from Tourette Syndrome Association Medical Advisory Board Treatment Guidelines** (with Usual Daily Dose Ranges) *(Gilbert D.; J Child Neurol; 2006; 21:690-700)*

<table>
<thead>
<tr>
<th>Category</th>
<th>Medication</th>
</tr>
</thead>
</table>
| **A: effective in 2 or more placebo-controlled trials** | Haloperidol, 1-4 mg  
Pimozide, 2-8 mg  
Risperidone, 1-4 mg |
| **B: effective in 1 placebo-controlled trial** | Fluphenazine, 1.5-10 mg  
Tiapride, 50-150 mg  
Ziprasidone, 20-80 mg  
Clonidine, 0.1-0.3 mg  
Guanfacine, 1-3 mg  
Pergolide, 0.1-0.45 mg  
Botulinum toxin, 30-300 units |
| **C: effective in open-label study** | Olanzapine, 2.5-12.5 mg  
Sulpiride, 200-1000 mg  
Tetrabenazine, 37.5-150 mg  
Baclofen, 40-60 mg  
Nicotine patch, 7-21 mg  
Mecamylamine, 2.5-7.5 mg  
*Aripiprazole, 2.5-10 mg.* |

## Non-Antipsychotic Drugs Used in the Treatment of Tics: Empirical Support and Dosing Guidelines

<table>
<thead>
<tr>
<th>Medication</th>
<th>Empirical Support</th>
<th>Starting Dose (mg)*</th>
<th>Usual Dose Range (mg/day)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clonidine</td>
<td>B</td>
<td>0.025-0.05</td>
<td>0.10-0.30</td>
</tr>
<tr>
<td>Guanfacine</td>
<td>B</td>
<td>0.5-1.0</td>
<td>1.0-3.0</td>
</tr>
<tr>
<td>Pergolide†</td>
<td>B</td>
<td>0.025</td>
<td>0.10-0.4</td>
</tr>
<tr>
<td>Botulinum toxin</td>
<td>B</td>
<td>30-300 units in one or more focal sites</td>
<td></td>
</tr>
<tr>
<td>Tetrabenazine</td>
<td>C</td>
<td>25</td>
<td>37.5-150</td>
</tr>
<tr>
<td>Baclofen</td>
<td>C</td>
<td>10</td>
<td>40-60</td>
</tr>
<tr>
<td>Nicotine Patch</td>
<td>C</td>
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<td>7-21</td>
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<tr>
<td>Mecamylamine</td>
<td>C</td>
<td>2.5</td>
<td>2.25-7.5</td>
</tr>
<tr>
<td>Flutamide</td>
<td>C</td>
<td>250</td>
<td>750‡</td>
</tr>
</tbody>
</table>

* Dose in mg unless otherwise specified.

† Second controlled study was superior to placebo only when tic-related impairment was included in the analysis.

‡ Only one controlled study, superior to placebo, but magnitude of effect was small.

Percent Improvement for Medications Showing Superiority to Placebo for the Treatment of Tics

<table>
<thead>
<tr>
<th>Drug</th>
<th>Improvement * (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clonidine</td>
<td>35</td>
</tr>
<tr>
<td>Guanfacine</td>
<td>30-37</td>
</tr>
<tr>
<td>Pergolide</td>
<td>35</td>
</tr>
<tr>
<td>Botulinum toxin</td>
<td>40</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>35</td>
</tr>
<tr>
<td>Risperidone</td>
<td>35-50</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>66</td>
</tr>
<tr>
<td>Pimozide</td>
<td>39-58</td>
</tr>
<tr>
<td>Tiapride</td>
<td>44</td>
</tr>
</tbody>
</table>

* Without Adjustment for Placebo

Scahill et al. 2006
Suggested Algorithm: Tics, Tourette’s and ADHD: ADHD is Primary Issue

Tics/TD + ADHD

ADHD
First Priority

Stimulant
Alpha agonist
Atomoxetine
Alpha agonist + stimulant
ADHD and Tics/TD: How To Prioritize Comorbid Disorders and Treatment

• For treatment of TD + ADHD, if ADHD symptoms are primary or most severe, consider:
  • 1) stimulant, with or without alpha agonist
  • 2) alpha agonist (or in combination with above)
  • 3) atomoxetine, with or without alpha agonist
  • 4) pramipexole ? (Levels A and B)
### Non-Stimulants Used in the Treatment of ADHD: Empirical Support and Dosing Guidelines

<table>
<thead>
<tr>
<th>Medication</th>
<th>Empirical Support</th>
<th>Starting Dose (mg)</th>
<th>Usual Dose Range (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Desipramine</td>
<td>A</td>
<td>10-25</td>
<td>50-150</td>
</tr>
<tr>
<td>Nortriptyline</td>
<td>C</td>
<td>10-25</td>
<td>20-100</td>
</tr>
<tr>
<td>Clonidine</td>
<td>B</td>
<td>0.025-0.05</td>
<td>0.15-0.3</td>
</tr>
<tr>
<td>Guanfacine</td>
<td>B</td>
<td>0.25-0.50</td>
<td>1.5-3.5</td>
</tr>
<tr>
<td>Bupropion</td>
<td>A</td>
<td>25-50</td>
<td>75-150</td>
</tr>
<tr>
<td>Deprenyl</td>
<td>B</td>
<td>5.0</td>
<td>5-15</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>B*</td>
<td>37.5</td>
<td>75-200</td>
</tr>
<tr>
<td>Atomoxetine</td>
<td>A</td>
<td>10-20</td>
<td>40-80</td>
</tr>
<tr>
<td>Pindolol</td>
<td>B</td>
<td>5-10</td>
<td>15-40</td>
</tr>
</tbody>
</table>

*Data in pediatric populations are limited.*

Scahill et al. 2006.
ADHD and Tics/TD: Can We Treat with Stimulants?

• *Old studies* suggested that stimulants increase tics, (Lowe et al. 1980) and pharmaceutical labeling states tics are a contraindication for stimulants (PDR, 2012)

• Long term methylphenidate treatment did not worsen tics in children with ADHD and multiple tic disorders (Castellanos et al. 1997)

• *More recent studies* demonstrated that some TD patients with significant ADHD may be candidates for methylphenidate (MPH) when no other treatments have been effective (Gadow, Nolan, Sverd. 1992; Gadow et al. 2007)
Onset of Tic Disorders in ADHD Probands
Stratified by Stimulant Treatment
(Spencer, Biederman, Coffey, et al. Arch Gen Psych 1999, 56: 842-847)
Offset of Tic Disorders in ADHD Probands
Stratified by Stimulant Treatment
(Spencer, Biederman, Coffey, et al. Arch Gen Psych 1999, 56: 842-847)
Treatment of ADHD and Tics (TACT): Targeted Combined Pharmacotherapy Study (TSSG. TACT. Neurology. 2002; 58:527-536)

• NINDS-sponsored multicenter study of clonidine and methylphenidate (MPH) in the treatment of children with ADHD and Tourette’s disorder or chronic tics (TACT)

• **Design:** 136 children (ages 7-14) were treated in the 16-week, double-blind, placebo-controlled protocol

  Hypotheses:

• *Methylphenidate and clonidine both individually and in combination are more effective than placebo* for treatment of ADHD and tics in Tourette’s Disorder

**Procedures:**

• Clonidine MPH Treatment Phase

• or Pbo or Pbo

• |-----------------|-----------------|-----------------|-----------------|

• BL 4 wk 8 wk 12 wk 16 wk
• **ADHD** (Teacher Conners): Compared to placebo, greatest benefit for CLON + MPH \((p < 0.0001)\); significant improvement in CLON \((p < 0.002)\) and MPH \((p < 0.003)\) groups
• **CLON**: best for hyperactivity and impulsivity; MPH for inattention
• **Tics** (YGTSS): severity reduced in all treatment groups vs. placebo; order was CLON + MPH > CLON > MPH
• **Mean doses of each drug were low:** 0.25 CLON / 26 MPH
• **Adverse Effects:** No difference in % of MPH (20%), CLON (26%) and PBO (22%) groups with worsening of tics
• There were **no safety issues**, particularly cardiovascular
Figure 2. Mean change from baseline on the Conners Ab-
**TD + ADHD: Alternative to Stimulants**

Atomoxetine Treatment in Children and Adolescents with ADHD and Comorbid Tic Disorders


- **Study design**: randomized controlled trial; non-inferiority hypothesis
- **Subjects**: children and adolescents 7-17 years old
- **Met DSM-IV criteria for ADHD and had concurrent Tourette’s Disorder or chronic motor tic disorder**
- **2-week screening and washout period followed by a 3-week dose-titration phase and a 15-week acute treatment phase**
- **Subjects were randomly assigned to double-blind treatment with either placebo or atomoxetine (0.5–1.5 mg/kg/day)**
Yale Global Tic Severity Scale (YGTSS) Tourette’s Subjects Only

Baseline:       23.0   23.6           13.6   13.2            9.4    10.4           22.7    21.4

Total         Motor        Phonic        Overall

Impairment

Mean Change from Baseline

Baseline: 23.0 23.6

Total     Motor        Phonic

Reduction in Symptoms

Atomoxetine Placebo

* p = .027
*p = .039
p = .126
*p = .019
Meta-Analysis: Treatment of Attention Deficit Hyperactivity Disorder in Children with Comorbid Tic Disorders
(Bloch, M. Panza, K. Landeros-Weisenberger, A. and Leckman, J. JAACAP. 2009; 48 (9);884-893)

- **Aim**: To determine relative efficacy of medications to treat ADHD and tic symptoms in children with both TD and ADHD.
- **Design**: PubMed search for all double blind, RCTs in children with ADHD and tics using random effects meta-analysis with standardized mean difference as primary outcome for effect size.
- **Results**: N=9 studies with 477 subjects. N=6 medications: dextroamphetamine, methylphenidate, alpha 2 agonists (clonidine and guanfacine), desipramine, atomoxetine, and deprenyl.
Meta-Analysis: Treatment of Attention Deficit Hyperactivity Disorder in Children with Comorbid Tic Disorders

(Bloch, M. Panza, K. Landeros-Weisenberger, A. and Leckman, J. JAACAP. 2009; 48 (9);884-893)

• **Results:** Methylphenidate, alpha 2 agonists, desipramine, and atomoxetine showed efficacy in improving ADHD symptoms in children with comorbid tics.

• Alpha agonists and atomoxetine significantly improved comorbid tics.

• Supra-therapeutic doses of dextroamphetamine increase tics.

• There is no evidence that methylphenidate worsened tic severity in the short term.
Methylphenidate effect on ADHD (A) and tic severity (B)

Bloch, JAACAP, 2009
Alpha-2 agonists effect on ADHD (A) and tic severity (B)

### A

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Effect Size (random) 95% CI</th>
<th>Weight %</th>
<th>Effect Size (random) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Singer</td>
<td></td>
<td>39.79</td>
<td>0.42 [0.07, 0.77]</td>
</tr>
<tr>
<td>Scahill</td>
<td></td>
<td>22.63</td>
<td>0.99 [0.46, 1.52]</td>
</tr>
<tr>
<td>TSSG</td>
<td></td>
<td>37.58</td>
<td>0.57 [0.21, 0.94]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td></td>
<td><strong>100.00</strong></td>
<td><strong>0.61 [0.32, 0.90]</strong></td>
</tr>
</tbody>
</table>

Test for heterogeneity: Chi² = 3.09, df = 2 (P = 0.21)  
I² = 35.4%

Test for overall effect: Z = 4.08 (P < 0.0001)

---

### B

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Effect Size (random) 95% CI</th>
<th>Weight %</th>
<th>Effect Size (random) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scahill</td>
<td></td>
<td>32.22</td>
<td>0.71 [0.18, 1.25]</td>
</tr>
<tr>
<td>TSSG</td>
<td></td>
<td>67.78</td>
<td>0.75 [0.39, 1.12]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td></td>
<td><strong>100.00</strong></td>
<td><strong>0.74 [0.44, 1.04]</strong></td>
</tr>
</tbody>
</table>

Test for heterogeneity: Chi² = 0.01, df = 1 (P = 0.90)  
I² = 0%

Test for overall effect: Z = 4.80 (P < 0.00001)

---

Bloch, JAACAP, 2009
Meta-Analysis: Effectiveness of medication in treating ADHD and tic disorders

Bloch, JAACAP, 2009
Meta-Analysis: Treatment of Attention Deficit Hyperactivity Disorder in Children with Comorbid Tic Disorders

(Bloch, M. Panza,K. Landeros-Weisenberger, A. and Leckman, J. JAACAP. 2009; 48 (9);884-893)

• **Conclusion**: Methylphenidate seems to offer the best and most immediate improvement of ADHD and does not seem to worsen tics.

• **Alpha agonists** offer the best combination of improvement in both tics and ADHD symptoms.

• **Atomoxetine and desipramine** provide additional evidence based treatment of ADHD in children with comorbid tics.

• **Supra-therapeutic doses of dextroamphetamine** should be avoided.
Comprehensive Behavioral Intervention for Tics Study (CBITS) or Habit Reversal Therapy (Piacentini, J. Woods, D. Scahill et al. JAMA; 2010;303 (19):1929-1937)

Two parallel studies compared behavior therapy to supportive therapy (ST)

Child study: 126 children (ages 9-17) with TD/CTD; JAMA; 2010

Adult study: 120 children and adults (ages 16+) with TD/CTD: completed; under review

Three phases:
1) Awareness training
2) Competing response training
3) Social support

**In CBITS child study, children with ADHD did not do as well as those without ADHD…….
Responder Status at Week 10: Effect Size 0.68
(CGI-Improvement = 1 or 2) Courtesy of Piacentini, J.
AACAP 2009

p < 0.0001
(Lyon, G. Samar, S. Conelea, C. et al JCAP; 2010; (4) 283-289)

Aim: To test whether single dose, immediate release (IR) dexmethylphenidate (d)-MPH can facilitate behavioral tic suppression in youth with ADHD and TD

Design: N=10 children in a random cross-over design were administered d-MPH on one visit and no medication on another. Following baseline assessment, subjects were reinforced for suppressing tics using a behavioral reinforcement tic suppression paradigm (Woods et al; 2005)
### Sociodemographic Data: Testing Tic Suppression

<table>
<thead>
<tr>
<th></th>
<th>Mean ± SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>12.7 ± 2.6</td>
<td>8–16</td>
</tr>
<tr>
<td>IQ</td>
<td>104 ± 13.3</td>
<td>85–118</td>
</tr>
<tr>
<td>dMPH dose (mg)</td>
<td>7.5 ± 3.1</td>
<td>2.5–12.5</td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>Male</td>
<td>9</td>
<td>90%</td>
</tr>
<tr>
<td>Hispanic</td>
<td>3</td>
<td>30%</td>
</tr>
<tr>
<td>White non-Hispanic</td>
<td>7</td>
<td>70%</td>
</tr>
<tr>
<td>Tourette’s disorder diagnosis</td>
<td>10</td>
<td>100%</td>
</tr>
<tr>
<td>ADHD diagnosis</td>
<td>10</td>
<td>100%</td>
</tr>
<tr>
<td>Combined type</td>
<td>5</td>
<td>50%</td>
</tr>
<tr>
<td>Inattentive type</td>
<td>5</td>
<td>50%</td>
</tr>
<tr>
<td>ADHD-RS</td>
<td>25.3 ± 10.8</td>
<td>9–43</td>
</tr>
<tr>
<td>Concomitant medications</td>
<td>7</td>
<td>70%</td>
</tr>
</tbody>
</table>

**Abbreviations:**  
SD = standard deviation; IQ = intelligence quotient; dMPH = dexmethylphenidate; ADHD = attention-deficit/hyperactivity disorder; ADHD-RS = ADHD Rating Scale.

Lyon, JCAP, 2010
Figure 1.

General Setup

Observation Room

Computer Display

Token Dispenser

Participant

Recording Equipment

Control Room

researcher
Testing Tic Suppression: Yale Global Tic Severity Scale Subscale Scores by Study Condition

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th></th>
<th>Nonmedication</th>
<th></th>
<th>Medication</th>
<th></th>
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<tbody>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>Range</td>
<td>Mean ± SD</td>
<td>Range</td>
<td>Mean ± SD</td>
<td>Range</td>
</tr>
<tr>
<td>Motor tic</td>
<td>13.2 ± 3.5</td>
<td>8–18</td>
<td>13.6 ± 2.9</td>
<td>9–19</td>
<td>12.1 ± 2.0</td>
<td>10–15</td>
</tr>
<tr>
<td>Vocal tic</td>
<td>10.6 ± 5.0</td>
<td>0–17</td>
<td>8.6 ± 4.8</td>
<td>0–15</td>
<td>4.9 ± 6.9</td>
<td>0–16</td>
</tr>
<tr>
<td>Total tic</td>
<td>23.8 ± 7.5</td>
<td>10–35</td>
<td>22.1 ± 7.6</td>
<td>9–34</td>
<td>17.0 ± 8.4</td>
<td>10–31</td>
</tr>
<tr>
<td>Impairment score</td>
<td>18.0 ± 8.9</td>
<td>10–40</td>
<td>22.8 ± 7.6</td>
<td>20–40</td>
<td>19.4 ± 9.4</td>
<td>10–40</td>
</tr>
<tr>
<td>Global severity</td>
<td>41.8 ± 13.4</td>
<td>20–64</td>
<td>45 ± 10.6</td>
<td>29–62</td>
<td>36.4 ± 15.2</td>
<td>20–63</td>
</tr>
</tbody>
</table>

Abbreviations: SD = standard deviation.

Lyon, JCAP, 2010
Testing Tic Suppression: Mean number of tics per minute under the non-medication and one-time dose of MPH conditions during the TSP

Lyon, JCAP, 2010
Results: Relative to no medication, tics were reduced when subjects were given a single dose of d-MPH.

Behavioral reinforcement of tic suppression resulted in lower tic rates compared to baseline, but d-MPH did not enhance this suppression.

Conclusion: Results indicate replication of prior studies of behavioral tic suppression in youth with TD without ADHD, and tic reduction (vs. exacerbation) with acute d-MPH challenge.
ADHD and Tics Study Underway: Improving Tic-Related Response Inhibition: Comparing the Effects of MPH + HRT in Children and Adolescents with ADHD and CTDs – Study Flow Diagram

### Study Flow Diagram

**PART A**

- **Pre-Study**
  - Phone Screen
  - Baseline Assessment ADHD and Tics
- **Baseline Day 1**
  - MPH Titration
- **Week 4-6**
  - ADHD and Tic Severity Assessment

**PART B**

- **Endpoint Week 14-16**
  - Behavioral Treatment
  - ADHD and Tic Severity Assessment
Evidence Based ADHD/Tics/TD Treatment Algorithm

ADHD + TD or Chronic Tic Disorder

- Tics Primary
  - Alpha Agonist
    - Effective: Monitor
    - Tics Increase: Add Alpha-Agonist or Switch to Atomoxetine
      - Effective: Monitor
      - Intolerable or Inadequate: Consider TCA, pramipexole

- ADHD Primary
  - Stimulant (MPH)
    - Effective: Monitor
    - Tics Increase: Add Alpha-Agonist or Switch to Atomoxetine
      - Effective: Monitor
      - Intolerable or Inadequate: Consider TCA, pramipexole
Tourette’s and Tic Disorders, ADHD and Comorbidity: Summary

**There is bi-directional overlap of ADHD and Tic Disorders.**

- Prevalence of ADHD in TD in clinically referred samples is 50-75%, and tics in ADHD patients 10-30%.
- ADHD symptoms persist, but tic symptoms tend to remit over time.
- Most clinically referred patients with ADHD and tic disorders will need treatment for ADHD, and tics may or may not need treatment.
- Alpha agonist is recommended as initial pharmacotherapy for ADHD + tics when tics are the primary issue.
- Stimulants alone or atomoxetine are indicated when ADHD is the primary issue.
- Recent meta analysis reveals that methylphenidate is effective in treatment of ADHD in children with ADHD and tics, and does not increase tics in the short run.
- If monotherapy is not effective, or limited by adverse effects, targeted combined pharmacotherapy with alpha agonist and stimulant is indicated.
- Future directions: studies of combination pharmacotherapy and behavioral treatment, long acting stimulants in ADHD/ tic disorders, pre- and post treatment imaging studies.
“If you’re happy and you know it, stick with your dosage.”
• **Tics and Tourette’s Clinical and Research Program**
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  Professor of Neurology and Child and Adolescent Psychiatry
• **Vilma Gabbay, M.D. M.S**
• Leon Levy Assistant Professor, Child and Adolescent Psychiatry,
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• **Resham Gellatly, B.A.** Research Assistant (supported by the Barasch Donor Award)
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• **Kevin Lam, M.D.**
• Adjunct Assistant Professor, Child and Adolescent Psychiatry; Second Year Resident
• **Sarah (Abbey) Matson**, Research Intern
• **Lindsay Farmer**, Research Intern