Psychopharmacology, 2021:
A Master Class

Child and Adolescent Psychopharmacology
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and Behavioral Sciences
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Disclosures
(Past 12 Months)

• American Academy of Child and Adolescent Psychiatry: Honoraria
• Children’s Medical Services: Pediatrics Behavioral Health Initiative; Florida state contract
• Emalex: Research Support
• Harvard Medical School /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

• Off label indications will be discussed
Child and Adolescent Psychopharmacology:
Learning Objectives: At the end of this session the participant should be able to:

1. Review **indications** for pharmacological treatment of pediatric onset psychiatric disorders
2. Discuss **guidelines** for treatment of pediatric onset psychiatric disorders
3. Review selected classic pharmacological studies and **recent research highlights** to apply to child and adolescent clinical practice
4. Understand **benefits and risks** of recommended psychopharmacological treatments for children and adolescents
Lifetime Prevalence of Mental Disorders in US Adolescents
(Merikangas, K. et al JAACAP; 2010; 49 (10); 980-989)

- **Design**: National Comorbidity Survey-Adolescent Supplement
- Face to face survey of 10,123 adolescents, age 13-18, in US
- **Results**: Anxiety disorders (32%), Behavior Disorders (19%), Mood Disorders (14%) and Substance Use Disorders (11%).
- Overall prevalence of disorders with severe impairment and/or distress was 22%.
- Median age of onset was earliest for anxiety (6), behavior (11), mood (13), and SUD (15).
- **Conclusion**: Common mental disorders in adults first emerge in youth.

FIGURE 1  Cumulative lifetime prevalence of major classes of DSM-IV disorders among adolescents (N = 10,123).
Review: General Principles of Use of Medication in Children and Adolescents

- Need for comprehensive evaluation
- Medication risks vs. benefits; risks of no treatment
- FDA “approval” for use of psychotropic agents in youth is for labeling, not indication
- Developmentally relevant side effects: cognitive, growth and development related
- Adequate trial in children and adolescents
- **Targeted combined pharmacotherapy** can be potentially beneficial…. through synergistic effects of more than one agent
- **Outline today: Selected classic and recent important studies; key take home points for clinical practice**
Attention Deficit Hyperactivity Disorder: A Primer

(Faraone, S. Nature Reviews/Disease Primers et al. 2015; (1) 1-23)

Figure 2 | The age-dependent decline and persistence of attention-deficit/hyperactivity disorder throughout the lifetime. Follow-up studies have assessed children with attention-deficit/hyperactivity disorder (ADHD) at multiple time points after their initial diagnosis. Although they document an age-dependent decline in ADHD symptoms, ADHD is also a highly persistent disorder when defined by the persistence of functional impairment or the persistence of subthreshold (three or fewer) impairing symptoms. By contrast, many patients remit full diagnostic criteria.
Real-Life Consequences of ADHD
(Chair Summit, February 2019; CMEOutfitters)


Survey of 500 community adults with ADHD compared with 501 age- and gender-matched controls; 36% of ADHD patients reported medication use.

*p ≤ .001; †p < .01


ADHD: MTA Results

All treatment arms found to be effective on an absolute basis

- Medication management alone
- Medication management + behavioral treatment

Nearly equally effective and superior to both:

- Behavioral treatment alone
- Community based treatment

(MTA Study Group, Arch Gen Psych, 1999)
Medications: Attention-Deficit Hyperactivity Disorder

Pharmacological Treatment

Stimulants
- Methylphenidate
- Amphetamines
- FDA Approved
- Atomoxetine
- FDA Approved

Alpha Agonists
- Guanfacine (XR)
- Clonidine (XR)
- FDA Approved
- Guan XR or Clon XR + stimulants
- FDA Approved

Antidepressants
- Bupropion
- Tricyclics

Modafinil
- FDA Approved
**Key Points: Stimulants**

*Practice Parameter for Assessment and Treatment of ADHD, JAACAP, 2007; 46; 894-921*

- **Indications**: Attention Deficit Hyperactivity Disorder (ADHD), all presentations.
- Evidence base for ADHD pharmacotherapy is of the strongest in psychiatry or general medicine
- **Stimulants** are the most widely studied and efficacious agents in child psychiatry.
- Level A evidence based data.
- Response rate 70-80%
- *All medications must be titrated to individual clinical response*

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**Methylphenidate Formulations**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Formulation</th>
<th>Release % IR/ER</th>
<th>Isomers d,l</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ritalin® (IR)</td>
<td>Tablet</td>
<td>100/0</td>
<td>1:1</td>
<td>~ 4 hours</td>
</tr>
<tr>
<td>Methylphenidate Chewable</td>
<td>Chewable Tablets</td>
<td>100/0</td>
<td>1:1</td>
<td>~ 4 hours</td>
</tr>
<tr>
<td>Methylphenidate Oral Solution</td>
<td>Oral Solution</td>
<td>100/0</td>
<td>1:1</td>
<td>~ 4 hours</td>
</tr>
<tr>
<td>Concerta®</td>
<td>Capsule</td>
<td>20/80</td>
<td>1:1</td>
<td>~ 10-12 hrs</td>
</tr>
<tr>
<td>Quillivant XR®</td>
<td>Capsule</td>
<td>20/80</td>
<td>1:1</td>
<td>~ 10-12 hrs</td>
</tr>
<tr>
<td>AptoNor XR®</td>
<td>Capsule</td>
<td>20/80</td>
<td>1:1</td>
<td>~ 13-16 hrs</td>
</tr>
<tr>
<td>Daytrana®</td>
<td>Patch</td>
<td>N/A</td>
<td>1:1</td>
<td>6-12 hours</td>
</tr>
<tr>
<td>Jornay PM®</td>
<td>Delayed Release</td>
<td>0/100</td>
<td>1:1</td>
<td>Start 8-10 hrs Duration ~ 10-12 hrs</td>
</tr>
</tbody>
</table>

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T.J. Spencer. Pharmacotherapy of ADHD Across the Lifecycle: Stimulants; 2021 mghcme.org
Amphetamine Formulations

<table>
<thead>
<tr>
<th>Medication</th>
<th>Formulation</th>
<th>Release %</th>
<th>Isomers</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dexedrine®</td>
<td>Tablet</td>
<td>100/0</td>
<td>1:0</td>
<td>~ 4-6 hours</td>
</tr>
<tr>
<td>Zenzedi®</td>
<td>Capsules</td>
<td>unknown</td>
<td>1:0</td>
<td>~ 6 hours</td>
</tr>
<tr>
<td>Dexedrine Spansules®</td>
<td>Tablet</td>
<td>100/0</td>
<td>1:1</td>
<td>~ 4-6 hours</td>
</tr>
<tr>
<td>Adderal® (IR)</td>
<td>Tablet</td>
<td>100/0</td>
<td>3:1</td>
<td>~ 4-6 hours</td>
</tr>
<tr>
<td>Evekeo®</td>
<td>ODT</td>
<td>100/0</td>
<td>1:1</td>
<td>~ 4-6 hours</td>
</tr>
<tr>
<td>Procentra®</td>
<td>Oral Solution</td>
<td>100/0</td>
<td>1:0</td>
<td>~ 4-6 hours</td>
</tr>
<tr>
<td>Adzenys XR ODT®</td>
<td>ODT</td>
<td>50/50</td>
<td>3:1</td>
<td>~ 12 hours</td>
</tr>
<tr>
<td>Adzenys ER® Liquid</td>
<td>Oral Solution</td>
<td>50/50</td>
<td>3:1</td>
<td>~ 12 hours</td>
</tr>
<tr>
<td>Dyanavel XR®</td>
<td>Oral Solution</td>
<td>unknown</td>
<td>3:2:1</td>
<td>~ 13 hours</td>
</tr>
<tr>
<td>Adderal XR®</td>
<td>Capsule</td>
<td>50/50</td>
<td>3:1</td>
<td>~ 12 hours</td>
</tr>
<tr>
<td>Mydayis®</td>
<td>Capsule</td>
<td>33/33/33</td>
<td>3:1</td>
<td>~ 16 hours</td>
</tr>
<tr>
<td>Vyvanse®</td>
<td>Capsule</td>
<td>Prodrug</td>
<td>1:0</td>
<td>~ 13 hours</td>
</tr>
<tr>
<td>Vyvanse Chewable®</td>
<td>Tablet</td>
<td>Prodrug</td>
<td>1:0</td>
<td>~ 13 hours</td>
</tr>
</tbody>
</table>

Stimulants: Adverse Effects
Screening for Cardiac Risk (AHA Guidelines)

Medical History:
Personal congenital or acquired cardiac disease
Cardiac symptoms: chest pain, palpitations, syncope, post exercise symptoms
Family history of premature cardiac disease (<50 years)
Medications that might prolong QTc

Evaluation: Routine physical exam
Blood pressure, heart rate at baseline and follow-up, particularly with adults
EKG may be helpful, but not mandatory in otherwise healthy child.
Recommended in adults.
Routine Holter, ECHO not necessary

Key Point: Monitor symptoms during treatment
ADHD: Non-Stimulants Through the Lifespan
(T. Wilens, MGH Child and Adolescent Psychopharmacology, March 2021)

Atomoxetine
FDA approval for youth and adults; less robust response if prior stimulants
May be helpful for ADHD plus:
- Oppositional defiant disorder
- Tic disorders
- Anxiety
- Substance use disorders

Alpha 2 agonists
Extended release versions for both clonidine and guanfacine; studied in youth and adults
May be helpful for ADHD plus:
- As above + emotional dysregulation
- May be combined as augmentation with stimulant partial responders

Others: Bupropion, TCAs, modafinil
Key Point/Best Treatment: Algorithm for Treatment of Uncomplicated ADHD  
(Adapted: Texas Consensus Panel; 2007)

- **Stage 1**: Monotherapy: MPH or DEX: short acting or long acting (most clinicians start with long acting)
- **Stage 2**: Monotherapy: Second stimulant in same category or one not used in Stage 1
- **Stage 3**: Monotherapy Alternative: Atomoxetine
- **Stage 4**: Long acting Alpha 2 agonist
- **Stage 4a**: Long acting alpha 2 agonist plus stimulant

Antipsychotics: Early Onset Schizophrenia and Autism Spectrum Disorder

“The voices in my head want to sing on ‘American Idol.’”
Double Blind Comparison of FGAs and SGAs in Early Onset Schizophrenia and Schizoaffective Disorder: Findings from the TEOSS Study

- **Design:** NIMH acute 8 week trial, then 44 week double blind maintenance phase for responders.
- **Primary outcome measure:** Responder status at endpoint. Responder=CGI-I score 1 or 2 + 20% reduction in PANSS score.
- **Sample:** N=119 youth, age 8-19 years. **Diagnosis:** Schizophrenia, schizoaffective disorder, or schizophreniform disorder
- **Results:** Random assignment to olanzapine was discontinued by DSMB for greater increase in weight without greater efficacy
  - N=57/119 subjects (47%) responded to treatment during acute phase.
  - Mean endpoint doses: molindone 59.9 mg; olanzapine 11.4 mg; risperidone 2.8 mg per day.
- **Marked difference in EFFICACY between the atypicals and mid-potency typical WAS NOT observed.**
- **Significant differences in tolerability WERE observed:** olanzapine was most likely associated with weight and metabolic changes, risperidone was intermediate, and molindone was least likely associated.
Treatment discontinuation in the 52-week combined acute and maintenance studies:
Results: 116 randomized acute; 54 maintenance, 14 completed (12%)

Treantment of Early Onset Schizophrenia
Second Generation Antipsychotics
(J. Tyson, MGH Child and Adolescent Psychopharmacology, March 2021)

- 6 Second generation antipsychotics are FDA approved for youth
- Generally more tolerable adverse effects than first generation

- Risperidone; age 13-17 Tablet, liquid Long acting injectable (LAI)
- Paliperidone; 12-17; XR; LAI
- Aripiprazole; 13-17; tablet; ODT; LAI; IM
- Olanzapine; 13-17; tablet; ODT, IM, LAI
- Quetiapine; 13-17; tablet; XR
- Lurasidone; 13-17; tablet
Treatment of Early Onset Schizophrenia
Second and First Generation Antipsychotics
(J. Tyson, MGH Child and Adolescent Psychopharmacology, March 2021)

• Clozapine: not approved for youth but has shown greater efficacy than other neuroleptics
• Newer antipsychotics are not approved for youth

• **First Generation**: chlorpromazine, haloperidol, perphenazine, thioridazine, thiothixene and trifluoperazine
• These are more likely to be associated with discontinuation than SGAs

• All antipsychotics have relatively similar efficacy, so choice of agent for any individual patient will be about expected side effect profile

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Key Points: Pediatric Mania

**Bipolar 1 (BP1)** disorder is a highly impairing mood disorder that often has onset before adulthood.

BP1 is characterized by periods of spontaneous, abnormally elevated mood and/or irritable mood.

It is associated with significant disability, suicide attempts and functional impairment.

Lithium has long been a benchmark treatment of adults with Bipolar 1, but there has been a lack of rigorous, well controlled investigation in pediatric patients.

But progress is being made…….

Table 1
Medications approved by the Food and Drug Administration for the treatment of pediatric bipolar disorder

<table>
<thead>
<tr>
<th>Medication</th>
<th>Phase of Bipolar Disorder</th>
<th>Age, y</th>
<th>Daily Dose Range, mg/d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lithium</td>
<td>Mixed/manic</td>
<td>12–17</td>
<td>300–2400</td>
</tr>
<tr>
<td>Risperidone</td>
<td>Mixed/manic</td>
<td>10–17</td>
<td>0.25–2.5</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>Mixed/manic</td>
<td>13–17</td>
<td>2.5–20</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>Mixed/manic</td>
<td>10–17</td>
<td>2–30</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>Mixed/manic</td>
<td>10–17</td>
<td>50–600</td>
</tr>
<tr>
<td>Olanzapine/fluoxetine combination</td>
<td>Depressive episode</td>
<td>10–17</td>
<td>3/25–12/50</td>
</tr>
</tbody>
</table>

Antipsychotic and Mood Stabilizer Efficacy in Pediatric and Adult Patients with Bipolar I Mania  
*(Correll, C. et al; Bipolar Disorders 2010; 12; 116-141)*

<table>
<thead>
<tr>
<th>Medication</th>
<th>Effect Size</th>
<th>Child (95% CI)</th>
<th>vs. Adult</th>
</tr>
</thead>
<tbody>
<tr>
<td>Divalproex-IR/ER</td>
<td>0.28</td>
<td>(0.01-0.54)</td>
<td>0.61</td>
</tr>
<tr>
<td>Lithium</td>
<td>0.31</td>
<td>(-0.12-0.73)</td>
<td>0.50</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>0.11</td>
<td>(-0.26-0.49)</td>
<td>N/A</td>
</tr>
<tr>
<td>Topiramate</td>
<td>0.51</td>
<td>(0.03-1.14)</td>
<td>0.05</td>
</tr>
<tr>
<td><strong>Weighted MS</strong></td>
<td><strong>0.24</strong></td>
<td><strong>(0.06-0.41)</strong></td>
<td><strong>0.46</strong></td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>0.69</td>
<td>(0.44-0.94)</td>
<td>0.36</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>0.75</td>
<td>(0.41-1.08)</td>
<td>0.48</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>0.60</td>
<td>(0.35-0.86)</td>
<td>0.52</td>
</tr>
<tr>
<td>Risperidone</td>
<td>0.81</td>
<td>(0.48-1.14)</td>
<td>0.71</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>0.48</td>
<td>(0.21-0.76)</td>
<td>0.42</td>
</tr>
<tr>
<td><strong>Weighted SGAs</strong></td>
<td><strong>0.65</strong></td>
<td><strong>(0.53-0.78)</strong></td>
<td><strong>0.48</strong></td>
</tr>
</tbody>
</table>
Key Points: Monitoring Youth on Antipsychotic Medication

Children and adolescents appear to be at increased risk for weight gain with antipsychotics compared to adults, which follows roughly the same rank order as in adults, but the magnitude is greater in youth. Start with aripiprazole, lurasidone or ziprasidone since associated weight gain and metabolic effects may be less than with other atypicals.

Before starting:
- Weight, Waist circumference and BMI
- Family History of Diabetes, Obesity, Hypertension and/or Cardiovascular Disease
- Lipid panel and Fasting Blood Sugar (FBS), Hg A1c

Monitor:
1) Weight, BP and BMI at 4, 8, 12 weeks and every 2-3 months going forward
2) FBS and lipid panel at 3 months and twice a year if normal
Key Points: Pediatric Depression

- Lifetime prevalence: National Comorbidity Survey
- Major depression/Dysthymia: 16% females; 8% males; severe impairment: 9%
- Acute treatment: only two medications are FDA approved for labeling:
  - Fluoxetine: age 8-17 (3 studies)
  - Escitalopram: age 12-17 (1 study)
- Treatment phases:
  - Acute: (6-12 weeks)
  - Continuation: relapse prevention (6-12 months)
  - Maintenance: recurrence prevention (> one year)

FDA Approved Treatments for Pediatric Acute Depression
(K. Wagner, MGH Child and Adolescent Psychopharmacology; March 2021)

<table>
<thead>
<tr>
<th>Medication</th>
<th>Ages</th>
<th>Number of Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoxetine</td>
<td>8-17</td>
<td>3</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>12-17</td>
<td>1</td>
</tr>
</tbody>
</table>
Treatment of Pediatric MDD: Acute
(Bridge, J. et al JAMA; 2007; Bridge, J. et al; Am J Psych 2009; 166; 42-49)

- All published and unpublished studies
- **Overall Response**: Antidepressants 40-70% vs. placebo 30-60%
- **Remission**: CDRS <28: 30-40%
- **Predictors of Poorer Response to Acute Treatment**
  (Emslie et al 2011; Goldstein et al 2007; Asarnow et al 2009)
  - More severe depression
  - Baseline suicidality
  - Comorbidity (anxiety and substance abuse)
  - Hopelessness
  - Family conflict

Treatment of Adolescent Depression Study (TADS)
(TADS Study Team; JAMA; 2004; 292; 7; 807-20)

- **Design**: NIMH multi-center, RCT of short term (12 weeks) and long term (36 weeks) efficacy of:
  - 1) fluoxetine 2) cognitive-behavior therapy (CBT) 3) combination 4) placebo (acute)
- **Methods**: Subjects: N=439 adolescents, age 12-17 with MDD
- **Primary outcome measures**: CDRS, CGI
- Flexible dosing schedule based on clinician CGI
- Starting dose 10 mg FL, to 40 mg, maximum 60 mg.
- **CBT**: Skills oriented; individual/family with manualized techniques: problem solving and cognitive restructuring.
- **Results**: N=378 completers; mean age 15 years
  - Combination FLX + CBT was superior to PBO on CDRS-R (p<0.001);
  - FLX alone (p<0.02) and CBT (P<0.01) alone
- **Adverse effects**: Patients became significantly less suicidal no matter what treatment; no suicides
- **Conclusion**: Benefits far outweigh risks
Adjusted Mean Mood (SE) Scale Scores for Participants in the TADS Study

CBT indicates cognitive-behavioral therapy. Means are for predicted individual scores that have been adjusted for both fixed (treatment and time) and random (participant and site) effects derived from the linear random-coefficient model.

**Figure 4** Comparison of children’s and adults’ responses to selective serotonin reuptake inhibitors (SSRIs) in major depressive disorder (MDD). Note: SMD = standardized mean difference. $p < .05$
Adolescent depression is a significant public health problem associated with significant morbidity and mortality. Nearly 40% of adolescents remain depressed after initial treatment, and over half of that population remain depressed despite switching medications or adding psychotherapy. There is limited pediatric evidence to guide clinicians as to how to proceed therapeutically with these treatment resistant patients, nor is there a clear, systemized method to identify them. Authors propose definitions of treatment resistant and treatment refractory depression, and review the evidence base regarding treatment strategies, comparing with the adult treatment literature. Authors propose a staging model of treatment resistance for pediatric depression, relevant both for clinical practice and for needed research.
<table>
<thead>
<tr>
<th></th>
<th>Pediatric</th>
<th>Adult</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Starting dose (mg/day)</td>
<td>Typical dose range (mg/day)</td>
</tr>
<tr>
<td>Selective serotonin reuptake inhibitors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Citalopram</td>
<td>10-20</td>
<td>20-40</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>10</td>
<td>10-20</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>10-20</td>
<td>20-80</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>25-50</td>
<td>50-300</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>10-20</td>
<td>20-60</td>
</tr>
<tr>
<td>Sertraline</td>
<td>25-50</td>
<td>100-200</td>
</tr>
<tr>
<td>Serotonin-norepinephrine reuptake inhibitors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>37.5</td>
<td>150-225</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>30</td>
<td>40-60</td>
</tr>
<tr>
<td>Desvenlafaxine</td>
<td>25</td>
<td>25-100</td>
</tr>
<tr>
<td>Atypical antidepressants</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bupropion</td>
<td>100</td>
<td>150-300</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>7.5-15</td>
<td>15-45</td>
</tr>
<tr>
<td>Vilazodone</td>
<td>5</td>
<td>10-20</td>
</tr>
<tr>
<td>Vortioxetine</td>
<td>5</td>
<td>10-20</td>
</tr>
</tbody>
</table>

(A) Adolescents with SSRI-resistant MDD

Switch to new SSRI
(citalopram, fluoxetine, paroxetine*;
20–40 mg/day)

Switch to SNRI
(venlafaxine;
150–225 mg/day)

+ CBT  No therapy  + CBT  No therapy

(B) TORDIA Take-home points:

1. Higher response rates with CBT with either medication class switch
2. Similar response rates with a switch to a different SSRI vs. switching to venlafaxine
3. However, venlafaxine has a significantly greater side effect burden than SSRIs

Antidepressant Treatment Duration in Pediatric Depression and Anxiety Disorders: How Long is Long Enough? (Hathaway, E. et al. Current Probl Pediatr Adolesc Health Care; (48); 2018; 31-39)

► **Method:** Systematic review of guidelines and clinical trial data on antidepressant (AD) treatment duration in pediatric patients with depressive and anxiety disorders.

► **Results:** Extant literature suggests 9-12 months of AD treatment for youth with major depressive disorder.

**Conclusion:** Evidence based guidelines represent a starting point, but appropriate treatment varies and individual factors must be considered.

<table>
<thead>
<tr>
<th>Major depressive disorder</th>
<th>Anxiety disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>More prior depressive episodes</td>
<td>Older age(^{15})</td>
</tr>
<tr>
<td>Residual symptoms after treatment (in adults)</td>
<td>Female sex(^{20})</td>
</tr>
<tr>
<td>Greater family levels of expressed emotion</td>
<td>Minority status(^{25})</td>
</tr>
<tr>
<td>Perceived family conflict</td>
<td>Baseline symptom severity(^{35,40})</td>
</tr>
<tr>
<td>Non-response to acute therapy (survey of outcomes following treatment for adolescent)</td>
<td>Lower socioeconomic status(^{10})</td>
</tr>
<tr>
<td>Depression study (unpublished)</td>
<td>Co-occurring internalizing disorder(^{25})</td>
</tr>
<tr>
<td>Female sex (survey of outcomes following treatment for adolescent depression study, unpublished)</td>
<td>Social anxiety disorder(^{25})</td>
</tr>
<tr>
<td></td>
<td>Greater negative life events</td>
</tr>
</tbody>
</table>

Practical Suggestions for Treatment of Pediatric Depression

- Complete a comprehensive evaluation with multiple informants and child/adolescent
- Evaluate suicidality (passive wishes to be dead, ideation, plan) and continue to monitor closely with C-SSRS
- Start with one of the FDA approved agents, ie fluoxetine in young children and fluoxetine or escitalopram in adolescents
- Start low (ie 10 mg fluoxetine, 5 mg escitalopram) and go slow to minimize adverse effects
- Monitor symptoms and response closely for first 8-12 weeks
- Until pharmacogenomics is ready for prime time, take a family history of relatives’ response to specific medication(s) which may be helpful in decision making
Overview: Treatment of Anxiety Disorders In Children and Adolescents
(Walkup, J. AACAP Psychopharmacology Update, 2015, 2018)

Children with mild-moderate symptoms should be started on psychosocial treatments first
Antidepressants work extremely well
**SSRIs are the treatment of choice**
Atypical antidepressants (bupropion, mirtazapine) should be considered second line, but considered
Some limited data on augmentation strategies
Limited data for benzodiazepines
*Off label prescribing is often necessary*

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**Child/Adolescent Anxiety Multimodal Study (CAMS)**
doi:10.1056/NEJMoa0804633)

- **Design**: NIMH-funded randomized, controlled trial comparing sertraline, CBT, combination and placebo
- **Results**: N=488
  - Mean age: 10-11 years
  - 12 week acute phase
  - 6 month follow-up
  - Mean dose ~140 mg/day
  - Response: Combination 81%; CBT 60%; Sertraline 56%; PBO 24%
- **Conclusion**: Combination treatment was most effective in treatment of childhood onset anxiety disorders, but both CBT and medication alone were more effective than placebo.
Treatment of Pediatric Anxiety Disorders: Serotonin Reuptake Inhibitors: 
FDA Approvals

- Clomipramine - FDA approved > age 10 OCD
- Fluvoxamine - FDA approved > age 8 OCD
- Sertraline - FDA approved > age 6 OCD
- Escitalopram – FDA approved > age 12 for depression
- Fluoxetine – effective for OCD; FDA approved MDD > age 7
- Paroxetine – effective for OCD and Social Phobia
- Citalopram – No controlled trials in children
Figure 2. Forest Plot of Medication Class Efficacy Relative to Placebo for Treatment Response (A) and Anxiety Symptom Improvement (B) and Funnel Plots for Treatment Response (C), Anxiety Symptom Improvement (D), All-Cause Discontinuation (E), and Discontinuation Due to Adverse Events (F)

A. Treatment Response

<table>
<thead>
<tr>
<th>Medication Class</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSRI (7)</td>
<td>4.6 (3.1 to 7.5)</td>
</tr>
<tr>
<td>SNRI (5)</td>
<td>2.4 (1.7 to 3.6)</td>
</tr>
<tr>
<td>TCA (4)</td>
<td>2.0 (0.8 to 4.9)</td>
</tr>
<tr>
<td>Benzo (2)</td>
<td>1.4 (0.3 to 6.1)</td>
</tr>
<tr>
<td>α2 Agonist (1)</td>
<td>5.6 (1.4 to 26.8)</td>
</tr>
<tr>
<td>5-HT1A Agonist (2)</td>
<td>1.3 (0.7 to 2.4)</td>
</tr>
</tbody>
</table>

Key Points: What Do the Studies Tell Us?
Guidelines to Treatment of Pediatric Anxiety Disorders

- Begin with CBT if symptoms are mild-moderate.
- For moderate to severe symptoms, begin with SSRI of choice, depending on family history response and side effect profile.
- Start low (i.e. 5-10 mg fluoxetine equivalents) and titrate gradually upward.
- Therapeutic response: In randomized controlled trials, onset around week 4; may be earlier in many youth.
- Second line: duloxetine, benzodiazepines, buspirone (augmentation), and tricyclic antidepressants.
- CAMS Follow up: Positive response to anxiety treatment in early childhood was associated with improved global functioning and life satisfaction in long term follow up.
Characteristics of Pediatric OCD

- Distinct pre-pubertal age of onset
- Male predominance
- Strong family history
- High comorbidity with tic disorders and ADHD
- May lack insight into unrealistic nature of thoughts
Overview of Treatment: Pediatric OCD
First Line: Cognitive Behavioral Therapy

Psychoeducation
Map and Externalize OCD
“Bossing” Back

*Exposure and response prevention*

*Exposure to anxiety provoking thought leads to urge to ritualize >>> compulsion
If response is prevented, anxiety not relieved, habituation will occur and obsession will diminish

**AACAP recommends CBT as first line treatment for mild-moderate pediatric OCD**

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**Pediatric OCD Treatment Study (POTS): CBT, Sertraline and Combination for Children and Adolescents with OCD**
*(Pediatric OCD Treatment Study Group; JAMA, 2004; 292; 16; 1969-1976)*

- **Design**: Randomized controlled trial in 3 US centers
- **Methods**: Duration: 12 wk.; ages 7-17
- **N**: 112 randomized; 97 completers
- **Results**: Each treatment alone SER (p <0.007); CBT (p <0.003), COM (p <0.001) was more effective than placebo.
- **Effect sizes**: COM 1.4; CBT 0.97; SER 0.67
- **Conclusion**: Combined treatment was superior to both SER alone (p<0.006) and CBT (p<0.008) alone.
- **Adverse Effects**: Generally well tolerated.
Weekly Adjusted Intent-to-Treat CY-BOCS Score, by Treatment Group

Range of possible scores for the Children’s Yale-Brown Obsessive-Compulsive Scale (CY-BOCS) is 0-40. Error bars indicate SE. Mean (SE) scores adjusted for fixed effects for treatment, site, days since baseline (linear time trend), and all 2- and 3-way interactions.

Medications used in the Treatment of OCD: Empirical Support and Dosing Guidelines

<table>
<thead>
<tr>
<th>Medication</th>
<th>Child</th>
<th>Adult</th>
<th>Starting Dose (mg)</th>
<th>Usual Dose Range (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clomipramine</td>
<td>A</td>
<td>A</td>
<td>25-50</td>
<td>100-250</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>A</td>
<td>A</td>
<td>5-20</td>
<td>10-60</td>
</tr>
<tr>
<td>Sertraline</td>
<td>A</td>
<td>A</td>
<td>25-50</td>
<td>50-250</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>A</td>
<td>A</td>
<td>25-50</td>
<td>50-350</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>B</td>
<td>A</td>
<td>5-10</td>
<td>10-60</td>
</tr>
<tr>
<td>Citalopram</td>
<td>B</td>
<td>A</td>
<td>5-10</td>
<td>20-60</td>
</tr>
<tr>
<td>Escitalopram*</td>
<td>B</td>
<td>A</td>
<td>5-10</td>
<td>10-20</td>
</tr>
</tbody>
</table>

* Not well studied in OCD, presumed to be similar in efficacy to citalopram.

Scahill et al. 2006
Pediatric OCD Treatment: General Guidelines

- AACAP Practice Parameters recommends **CBT treatment as first line in mild-moderate OCD**
- **Uncomplicated OCD:**
  - Adequate trial of at least 2 SSRI/SRI agents sequentially.
  - *Duration: 8-10 weeks in juveniles at therapeutic dose.*
  - Maintenance: 6-12 months after response
- **Complicated OCD:**
  - Treatment of all comorbid disorders is necessary, prioritizing symptoms/disorders
  
**OCD + Tics** *(March et al. Biol Psych 2007; 61; 344-347)*

In POTS I, 15% had tics (TD or CMT). **Tics moderated response to SER** (no different than PBO,) but not to CBT or COM. Recommend start CBT or COMB.

OCD Pharmacotherapy: Duration of Treatment

- Optimal duration: **at least 10-12 weeks**
- Probably reasonable to begin with fluoxetine
- Relapses are common when medication is discontinued
- Probably reasonable to **maintain for 9-12 months** after treatment response
- Medication should be gradually tapered
- Adverse effects: gastrointestinal, activation, apathy (abulia)
**DSM 5: Neurodevelopmental Disorders: Motor Disorders: Tic Disorders**

**Provisional tic disorder:**
Single or multiple motor tics and/or vocal tics
Tics have been present for less than 1 year since first tic onset.
Onset is before age 18 years

**Persistent (Chronic) motor or vocal tic disorder:**
Single or multiple motor tics and/or vocal tics have been present during the illness, but **not both** motor and vocal.
The tics may wax and wane in frequency, but have persisted for more than 1 year since first tic onset

**Tourette’s Disorder (Tourette Syndrome):**
Both **multiple motor and one or more vocal tics** have been present at some time during the illness, although not necessarily concurrently.
The tics may wax and wane in frequency but have persisted for more than 1 year since first tic onset.

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**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.

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The Challenges of Treating Tics!
Roessner et al. Eur Child Adolesc Psychiatry; (2011); 20:173-196

Tourette Syndrome: Treatment Overview

Only formally approved (labeled) pharmacotherapy treatments for TD:

**D2 dopamine antagonists: neuroleptic medication**

*Haloperidol and pimozide* (Physicians Desk Reference, 2017)

**Haloperidol**: effective for tics, superior to placebo
(Shapiro, A. et al. 1968, 1978)

**Pimozide**: effective for tics, superior to placebo and haloperidol

* **Aripiprazole**: effective for tics, superior to placebo
(Yoo, H et al; 2013)
Daily Doses of Frequently Prescribed Tic Medications

<table>
<thead>
<tr>
<th>Medication</th>
<th>Range of daily dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haloperidol</td>
<td>0.25-4.0mg</td>
</tr>
<tr>
<td>Pimozide</td>
<td>0.5-8.0mg</td>
</tr>
<tr>
<td>*Risperidone</td>
<td>0.125-3.0mg</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>1.0-15.0mg</td>
</tr>
<tr>
<td>*Clonidine</td>
<td>0.025-0.4mg</td>
</tr>
<tr>
<td>*Guanfacine</td>
<td>0.25-4.0mg</td>
</tr>
</tbody>
</table>

Why a need for novel pharmacological treatments for TS?

Labeled for indication: D2 dopamine blockers have potential major adverse effects.
First generation neuroleptics: extrapyramidal effects
Second generation antipsychotics: metabolic effects
Off label agents: alpha adrenergic agonists: less effective; response moderated by ADHD. Fatigue, somnolence, and cardiovascular effects.

Comprehensive Behavioral Intervention for Tics (CBIT): lack of trained therapists; duration of treatment may be a problem for some....
- VMAT-2 inhibition depletes dopamine, reducing involuntary movements
- Clinically validated by efficacy of VMAT-2 inhibitors (reserpine, tetrabenazine)


1. Dopamine is stored into synaptic vesicles via the VMAT2 and stored until its release into the synapse.
2. Dopamine released during neurotransmission acts on 5 types of postsynaptic receptors (D1-D5).
3. The presynaptic D2 mesoreceptor acts as a negative feedback mechanism regulating the release of dopamine from the pre-synaptic neuron.

“If you’re happy and you know it, stick with your dosage.”

THURSDAY 25
SEPTEMBER
Psychiatric disorders are highly prevalent in youth.
- ADHD generally persists; some symptoms may attenuate over time.
- Stimulants are among the most effective medications in medicine and are generally safe.
- Several new stimulant delivery systems are now available.
- Non-stimulants are also effective for ADHD.
- Several SGAs in youth are approved for treatment of early onset schizophrenia and bipolar disorder.
- SGAs appear more effective in Bipolar I disorder than mood stabilizers, but youth may be more vulnerable to metabolic effects.
- MDD tends to be persistent and may be disabling. At least 9-12 months of antidepressant treatment is necessary, but individual response varies.. Children tend to have less robust a response than adults.
- SSRIs are effective treatments for anxiety disorders. For GAD, SAD, and Social AD, 6-9 months of anxiolytic treatment may be sufficient, although treatment may need to be extended to 12 months.
- For OCD, several SSRIs have been approved for use in youth. Clomipramine is a good alternative for those who do not respond to two SSRI adequate trials.
- Alpha adrenergic agonists are first line pharmacotherapy for tic disorders, but new clinical trials are underway.
- Tune in next year!