Living Legends in Psychopharmacology: From Current Evidence Base to Advances in Treatment

Child and Adolescent Psychopharmacology: Current Treatment for Best Practices

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Disclosures

(Past 24 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/NINDS: 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; CDC Partnership

- ***Off label indications will be discussed***

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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.

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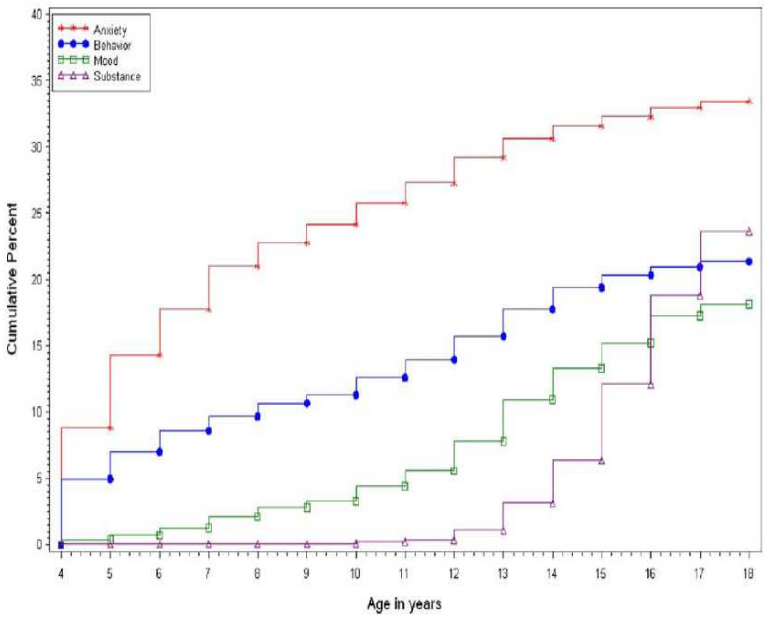
FIGURE 1 Cumulative lifetime prevalence of major classes of *DSM-IV* disorders among adolescents (N = 10,123).



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***

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Safety of 80 Antidepressants, Antipsychotics, ADHD Medications and Mood Stabilizers in Children and Adolescents with Psychiatric Disorders: A Large Scale Systematic Meta-review of 78 Adverse Effects

(*Marco Solmi, Michele Fornaro, Edoardo G. Ostinelli; World Psychiatry 2020;19:214–232)*

For this meta-review, we systematically searched network meta-analyses and meta-analyses of randomized controlled trials (RCTs), individual RCTs, and cohort studies reporting on **78 a priori selected adverse events** across 19 categories of 80 psychotropic medications in children and adolescents with mental disorders.

We included data from **nine network meta-analyses, 39 meta-analyses, 90 individual RCTs, and eight cohort studies, including 337,686 children and adolescents.**

Data on ≥20% of the 78 adverse events were available for six antidepressants (sertraline, escitalopram, paroxetine, fluoxetine, venlafaxine and vilazodone), eight antipsychotics (risperidone, quetiapine, aripiprazole, lurasidone, paliperidone, ziprasidone, olanzapine and asenapine), three anti-ADHD medications (methylphenidate, atomoxetine and guanfacine), and two mood stabilizers (valproate and lithium).

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Among medications with data on ≥20% of the 78 adverse events, a **safer profile emerged for escitalopram and fluoxetine among antidepressants, lurasidone for antipsychotics, methylphenidate among anti-ADHD medications, and lithium among mood stabilizers.**

The available literature raised **most concerns about the safety of venlafaxine, olanzapine, atomoxetine, guanfacine and valproate**. Nausea/vomiting and discontinuation due to adverse event were most frequently associated with antidepressants; sedation, extrapyramidal side effects, and weight gain with antipsychotics; anorexia and insomnia with anti-ADHD medications; sedation and weight gain with mood stabilizers.

The results of this comprehensive and updated quantitative systematic meta-review of top-tier evidence regarding the safety of antidepressants, antipsychotics, anti-ADHD medications and mood stabilizers in children and adolescents can inform clinical practice, research and treatment guidelines.

Attention Deficit Hyperactivity Disorder: A Primer

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

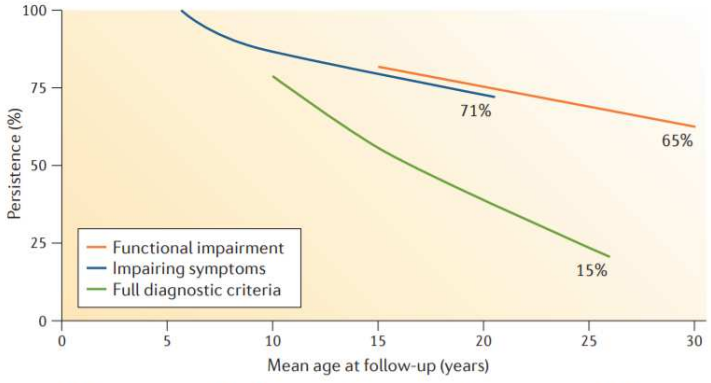
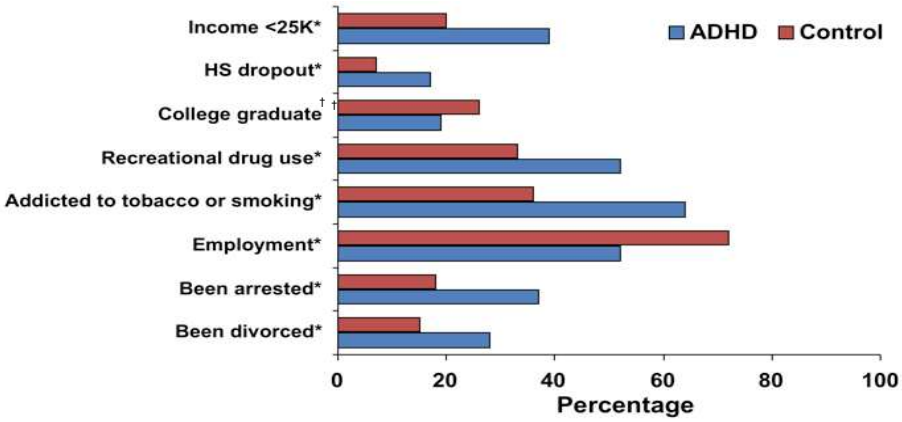


Figure 2 | **The age-dependent decline and persistence of attention-deficit/hyperactivity disorder throughout the lifetime.** Follow-up studies have assessed children with attention-deficit/hyperactivity disorder (ADHD) at multiple time points after their initial diagnosis. Although they document an age-dependent decline in ADHD symptoms, ADHD is also a highly persistent disorder when defined by the persistence of functional impairment[7] or the persistence of subthreshold (three or fewer) impairing symptoms[8]. By contrast, many patients remit full diagnostic criteria[7].

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.

*$p \leq .001$; †$p < .01$

Biederman J, et al. *J Clin Psychiatry*. 2006;67(4):524-540; Biederman J, et al. *MedGenMed*. 2006;8(3):12.

A Literature Review and Meta-analysis on the Effects of ADHD Medications on Functional Outcomes

(*Boland H, DiSalvo M, Fried R, Woodworth KY, Wilens T, Faraone SV, Biederman J. J Psychiatr Res. 2020 Apr;123:21-30. doi: 10.1016/j.jpsychires.2020.01.006. Epub 2020 Jan 27. PMID: 32014701*).

- **Objective:** Systematic review and meta-analysis of literature from large databases and registries to assess the effects of ADHD medication on associated functional outcomes.
- **Study design:** PubMed, PsycINFO, MEDLINE, and Web of Science literature review prior to January 2019. Sample size, age range, country of origin, medication type, number of functional events and non-events, odds ratios and hazard ratios, and means and standard deviations were extracted.
- **Results:** 40 articles were included. The majority suggest a **robust protective effect of ADHD medication treatment** on mood disorders, suicidality, criminality, substance use disorders, accidents and injuries, traumatic brain injuries, motor vehicle crashes, and educational outcomes.
- Similarly, the meta-analyses demonstrated a **protective effect of medication treatment on academic outcomes, accidents and injuries, and mood disorders.**
- **Conclusions:** These findings suggest that ADHD medication treatments are associated with decreases in the risks for a wide range of ADHD-associated functional outcomes supporting efforts aimed at early diagnosis and treatment of individuals with ADHD.

Figure 2. Odds ratio forest plot.

(H. Boland, et al., 2020)

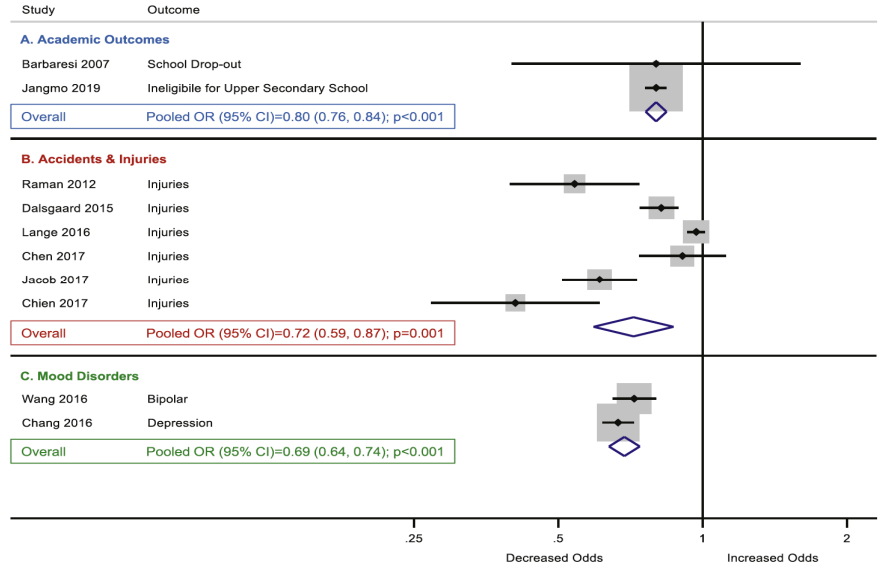


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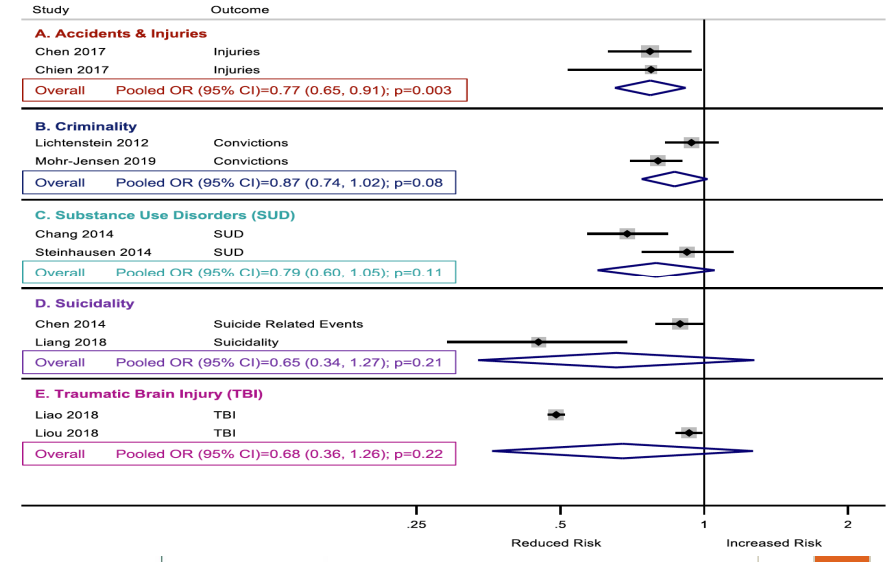
Figure 3. Hazard ratio forest plot.

(H. Boland, et al., 2020)



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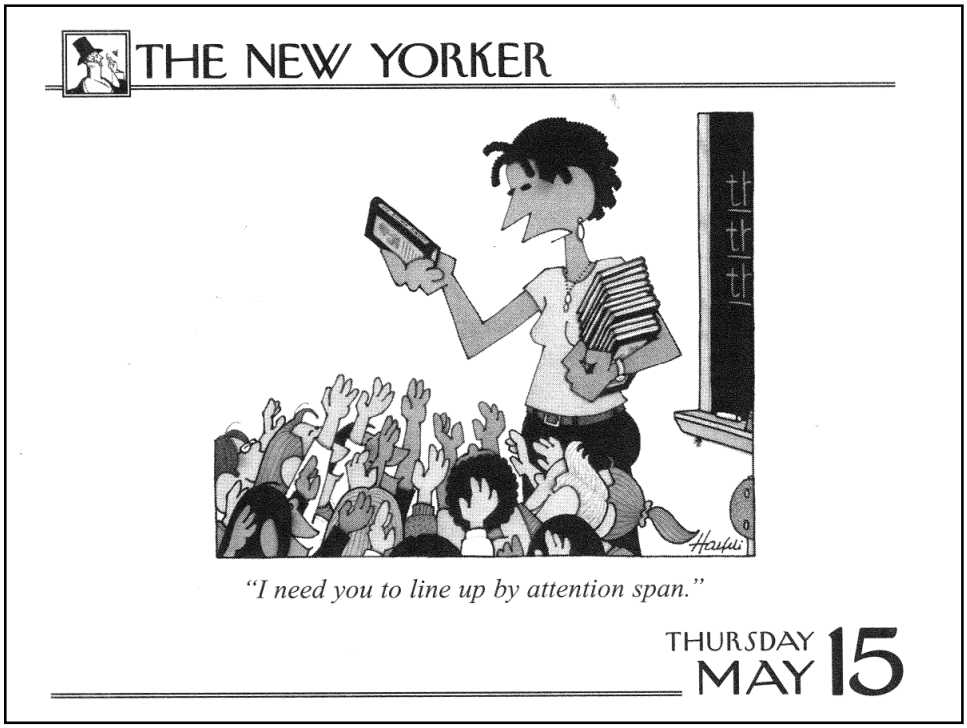

Medications: Attention-Deficit Hyperactivity Disorder

(ADHD in Children & Adults. Adler, L. Spencer, T. Wilens, T. (eds), Cambridge Press; 2015)

Pharmacological Treatment

- Stimulants
  - Methylphenidate
  - Amphetamines
  - ← FDA Approved
- Atomoxetine ← FDA Approved
- Alpha Agonists ← FDA Approved
  - Guanfacine (XR)
  - Clonidine (XR)
  - Guan XR or Clon XR + stimulants ← FDA Approved
- Antidepressants
  - Bupropion
  - Tricyclics
- Modafinil

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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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)

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New Formulations of Stimulants: An Update for Clinicians

(Steingard, R. et al. Journal of Child and Adolescent Psychopharm; 29; 2019; 324-339)

- There has been a **marked increase** in the number of available stimulant formulations.
- All these formulations involve changes to the pharmaceutical **delivery systems** of the two existing compounds: amphetamine (AMP) and methylphenidate (MPH).
- In the absence of reliable biomarkers that predict individualized response to ADHD treatment, clinical knowledge about differences in MPH and AMP pharmacodynamics, pharmacokinetics, and metabolism can be utilized to **personalize treatment** and optimize response.
- To manage the broad range of options that are now available, **clinicians should familiarize themselves** with each of these categories for both stimulant compounds.

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Methylphenidate Formulations

Medication	Formulation	Release % IR/ER	Isomers d,l	Duration
Ritalin® (IR)	Tablet	100/0	1:1	~ 4 hours
Methylin® Chewable	Chewable Tablets	100/0	1:1	~ 4 hours
Methylin® Oral Solution	Oral Solution	100/0	1:1	~ 4 hours
Focalin® (IR)	Tablet	100/0	1:0	~ 4 hours
Ritalin LA®	Capsule	50/50	1:1	~ 8 hours
Metadate CD®	Capsule	30/70	1:1	~ 8 hours
Focalin XR®	Capsule	50/50	1:0	~ 8-10 hours
Cotempla XR-ODT®	ODT	30/70	1:1	~ 8-12 hours
Quillichew ER®	Chewable Tablet	30/70	1:1	~ 8-10 hours
Concerta®	Capsule	22/78	1:1	~ 12 hours
Quillivant XR®	Oral Solution	20/80	1:1	~ 10-12 hrs
Aptensio XR®	Capsule	37/63	1:1	~ 12 hours
Adhansia XR®	Capsule	20/80	1:1	~ 13-16 hrs
Daytrana®	Patch	N/A	1:1	6-16 hours
Jornay PM®	Delayed Release Capsule	0/100	1:1	Start 8-10 hrs Duration ~ 10-12 hrs

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

Amphetamine Formulations

Medication	Formulation	Release % IR/ER	Isomers d,l	Duration
Dexedrine® Zenzedi®	Tablet	100/0	1:0	~ 4-6 hours
Dexedrine Spansules®	Capsules	unknown	1:0	~ 6 hours
Adderall® (IR)	Tablet	100/0	3:1	~ 4-6 hours
Evekeo®	Tablet	100/0	1:1	~ 4-6 hours
Evekeo ODT®	ODT	100/0	1:1	~ 4-6 hours
Procentra®	Oral Solution	100/0	1:0	~ 4-6 hours
Adzenys XR ODT®	ODT	50/50	3:1	~ 12 hours
Adzenys ER® Liquid	Oral Solution	50/50	3:1	~ 12 hours
Dyanavel XR®	Oral Solution	unknown	3.2:1	~ 13 hours
Adderall XR®	Capsule	50/50	3:1	~ 12 hours
Mydayis®	Capsule	33/33/33	3:1	~ 16 hours
Vyvanse®	Capsule	Prodrug	1:0	~ 13 hours
Vyvanse Chewable®	Tablet	Prodrug	1:0	~ 13 hours

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

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

(T. Spencer, T. Wilens, MGH Psychopharmacology, March 2016; 2018)

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

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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 stimulant exposure

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 augmentation with stimulant partial responders

Others: Bupropion, TCAs, modafinil

TABLE 1 ADHD Medication Effect Size

	Effect Size
Stimulant medications	1.0[a]
α-Agonist medications, ER	0.7
Atomoxetine	0.7

Data from ref 10. 0.2 = small effect size, 0.5 = moderate effect size, 0.8 = large effect size.

[a] 0.4–0.8 in preschoolers.

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ADHD: Clinical Practice Guideline for the Diagnosis, Evaluation, and Treatment of Attention-Deficit/Hyperactivity Disorder in Children and Adolescents

Summary of Key Action Statements

Wolraich ML, Hagan JF Jr, Allan C, Cha E,; SUBCOMMITTEE ON CHILDREN AND ADOLESCENTS WITH ATTENTION-DEFICIT/HYPERACTIVE DISORDER. Clinical Practice Guideline for the Diagnosis, Evaluation, and Treatment of Attention-Deficit/Hyperactivity Disorder in Children and Adolescents. Pediatrics. 2019 Oct;144(4):e20192528. doi: 10.1542/peds.2019-2528.

1. The primary care clinician should initiate **an evaluation for ADHD for any child 4 through 18 years** of age who presents with academic or behavioral problems and symptoms of inattention, hyperactivity, or impulsivity (quality of evidence B/strong recommendation).
2. To make a diagnosis of ADHD, the primary care clinician should determine that Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria have been met (including documentation of impairment in more than 1 major setting); information should be obtained primarily from reports from parents or guardians, teachers, and other school and mental health clinicians involved in the child's care. The primary care clinician should also rule out any alternative cause (quality of evidence B/strong recommendation).
3. In the evaluation of a child for ADHD, **the primary care clinician should include assessment for other conditions that might coexist with ADHD,** including emotional or behavioral (eg, anxiety, depressive, oppositional defiant, and conduct disorders), developmental (eg, learning and language disorders or other neurodevelopmental disorders), and physical (eg, tics, sleep apnea) conditions (quality of evidence B/strong recommendation).

ADHD: Clinical Practice Guideline for the Diagnosis, Evaluation, and Treatment of Attention-Deficit/Hyperactivity Disorder in Children and Adolescents

Summary of Key Action Statements

4. The primary care clinician should **recognize ADHD as a chronic condition and, therefore, consider children and adolescents with ADHD as children and youth with special health care needs. Management of children and youth with special health care needs should follow the principles of the chronic care model and the medical home (quality of evidence B/strong recommendation).**
5. Recommendations for treatment of children and youth with ADHD vary depending on the patient's age:
   a) **For *preschool-aged children*** *(4–5 years of age)*, prescribe evidence-based **parent- and/or teacher-administered behavior therapy as the first line of treatment** (quality of evidence A/strong recommendation) **and may prescribe methylphenidate if the behavior interventions do not provide significant improvement** and there is moderate-to-severe continuing disturbance in the child's function. In areas where evidence-based behavioral treatments are not available, the clinician needs to weigh the risks of starting medication at an early age against the harm of delaying diagnosis and treatment (quality of evidence B/recommendation).
   b) **For *elementary school–aged children (*** *6–11 years of age)*, the primary care clinician should **prescribe US Food and Drug Administration–approved medications for ADHD (quality of evidence A/strong recommendation) and/or evidence-based parent- and/or teacher-administered behavior therapy as treatment for ADHD, preferably both** (quality of evidence B/strong recommendation). The evidence is particularly strong for stimulant medications and sufficient but less strong for atomoxetine, extended-release guanfacine, and extended-release clonidine (in that order) (quality of evidence A/strong recommendation). The school environment, program, or placement is a part of any treatment plan.
   c) **For *adolescents (12–18 years of age),*** the primary care clinician should **prescribe Food and Drug Administration–approved medications for ADHD with the assent of the adolescent (quality of evidence A/strong recommendation) and may prescribe behavior therapy as treatment for ADHD (quality of evidence C/recommendation), preferably both**.
6. The primary care clinician should titrate doses of medication for ADHD to achieve maximum benefit with minimum adverse effects (quality of evidence B/strong recommendation).

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

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Antipsychotics: Early Onset Schizophrenia and Autism Spectrum Disorder

"The voices in my head want to sing on 'American Idol.'"

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Double Blind Comparison of FGAs and SGAs in Early Onset Schizophrenia and Schizoaffective Disorder: Findings from the TEOSS Study
(Sikich, L. Frazier, J. McClellan, J. et al. Am J Psych 2008; 165; 1420-1431)

- **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.

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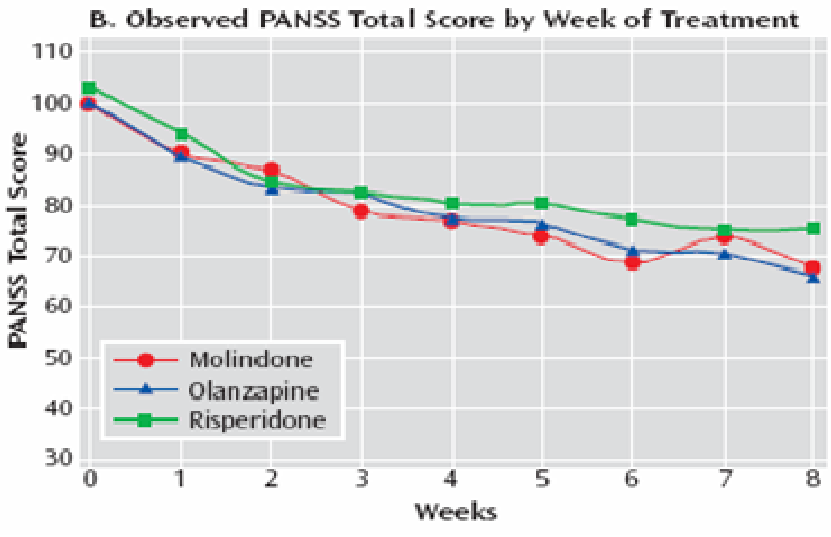
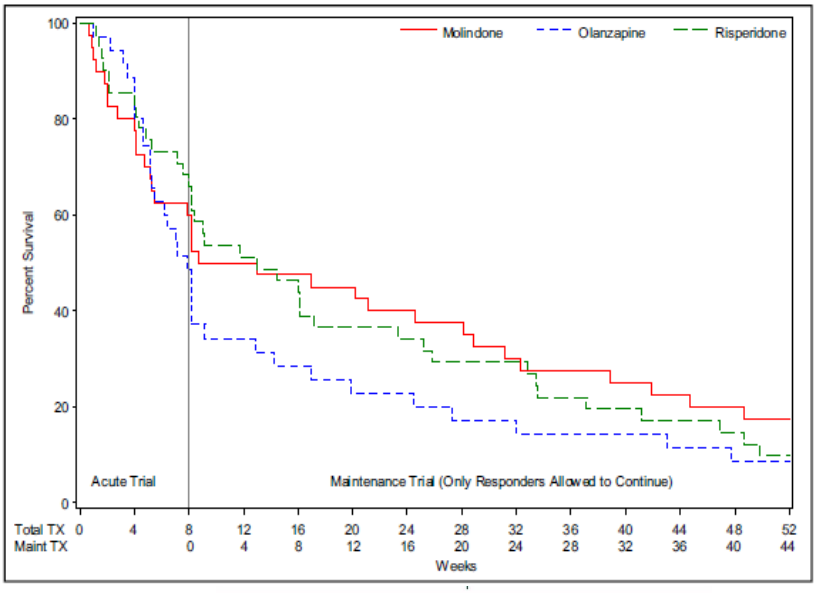


(Sikich, L. Frazier, J. McClellan, J. et al. Am J Psych 2008; 165; 1420-1431)

Treatment discontinuation in the 52-week combined acute and maintenance studies:
Results: 116 randomized acute; 54 maintenance, 14 completed (12%)



DB Maintenance Safety/Effectiveness in TEOSS. Findling, R. et al, JAACAP; 2010, 49 (6); 583-594.

Treatment 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
- For the most part, 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
- 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.**

Key Points and Practical Guidelines: DMDD vs. Pediatric Mania

Disruptive Mood Dysregulation Disorder (DMDD): arrived in DSM 5 in 2013.

Childhood onset mood disorder: characterized by **persistent irritability** or angry mood punctuated by frequent and disproportionately **severe temper outbursts.** Diagnosed in children older than age 6 with onset before age 10. Minimum duration of symptoms one year.

Thought to **reduce over-diagnosis of pediatric bipolar disorder and reduce antipsychotic use.**

Key point: High comorbidity with ADHD. Current practice, until more data is available, suggests that it is reasonable to treat ADHD optimally first. Optimize ADHD treatment and review residual symptoms. Combination stimulant and SSRI or low dose neuroleptic can be used.

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Diagnostic Trends and Prescription Patterns in Disruptive Mood Dysregulation Disorder and Bipolar Disorder

(Findling, R. et al. J Am Acad Child Adolesc Psychiatry; 2021)

Objective: Disruptive mood dysregulation disorder (DMDD) was introduced in *DSM-5* to distinguish a subset of chronically irritable youth who may be incorrectly diagnosed and/or treated for pediatric bipolar disorder (BPD). This study characterized the rate of new treatment episodes and treated prevalence of BPD and DMDD from a longitudinal electronic health record database and examined the impact of DMDD on prescription trends.

Method: A retrospective cohort study using 2008–2018 Optum electronic health record data was conducted. Youth aged 10 to < 18 years with ≥ 183 days of database enrollment before the study cohort entry were included. Annual new treatment episode rates per 1,000 patient-years and treated prevalence (%) were estimated. Prescriptions for medications, concomitant diagnoses, and acute mental health service use for 2016–2018 were evaluated.

Results: There were 7,677 youths with DMDD and 6,480 youths with BPD identified. Mean age (13–15 years) and ethnicity were similar for both groups. A rise in new treatment episode rates (0.87–1.75 per 1,000 patient-years, $p < .0001$) and treated prevalence (0.08%–0.35%, $p < .0001$) of DMDD diagnoses (2016–2018) following diagnosis inception was paralleled by decreasing new treatment episode rates (1.22–1.14 per 1,000 patient-years, $p < .01$) and treated prevalence (0.42%–0.36%, $p < .0001$) of BPD diagnoses (2015–2018). More youth in the DMDD group were prescribed medications compared with the BPD group (81.9% vs 69.4%), including antipsychotics (58.9% vs 51.0%). Higher proportions of youth with DMDD vs youth with BPD had disruptive behavior disorders (eg, 35.9% vs 20.5% had oppositional defiant disorder), and required inpatient hospitalization related to their mental health disorder (45.0% vs 33.0%).

Conclusion: Diagnosis of DMDD has had rapid uptake in clinical practice but is associated with increased antipsychotic and polypharmacy prescriptions and higher rates of comorbidity and inpatient hospitalization in youth with a DMDD diagnosis compared with a BPD diagnosis.

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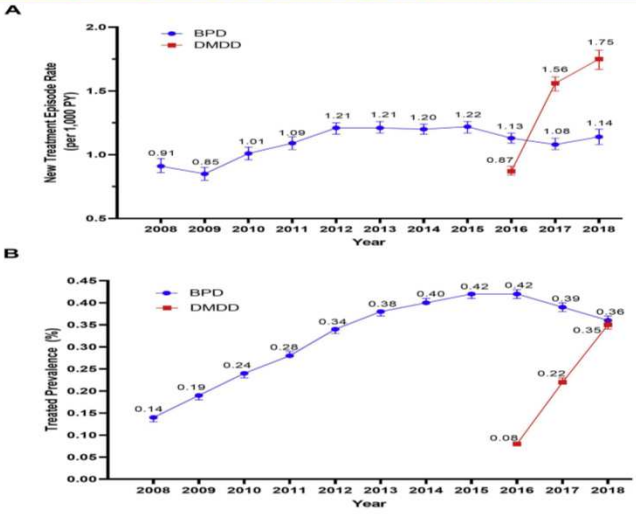
FIGURE 1 New Treatment Episode Rates and Treated Prevalence of Pediatric Bipolar Disorder (BPD) and Disruptive Mood Dysregulation Disorder (DMDD) Among Youth 10 to <18 Years of Age in the United States



Note: (A) New treatment episode rates per 1,000 PY of BPD (2008–2018) and DMDD (2016–2018). (B) Annual treated prevalence (%) of BPD (2008–2018) and DMDD (2016–2018). Error bars reflect 95% CIs. Some 95% CIs in panel (B) are obscured by the main data points. PY = patient-years. Please note color figures are available online.

(Findling, R. et al. J Am Acad Child Adolesc Psychiatry; 2021)

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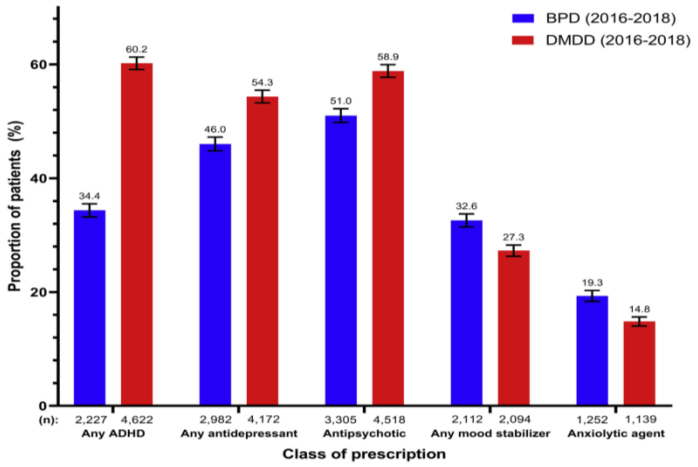
FIGURE 2 Comparison of Concurrent Prescriptions to Patients With Disruptive Mood Dysregulation Disorder (DMDD) or Pediatric Bipolar Disorder (BPD) Diagnoses by Drug Class for 2016–2018 (Within 6 Months Before and Following the New Treatment Episode)



Note: Antipsychotic/antidepressant combination drugs not included because there were only 4 documented prescriptions in this class of medications. Error bars reflect 95% CIs. ADHD = attention-deficit/hyperactivity disorder. Please note color figures are available online.

(Findling, R. et al. J Am Acad Child Adolesc Psychiatry; 2021)

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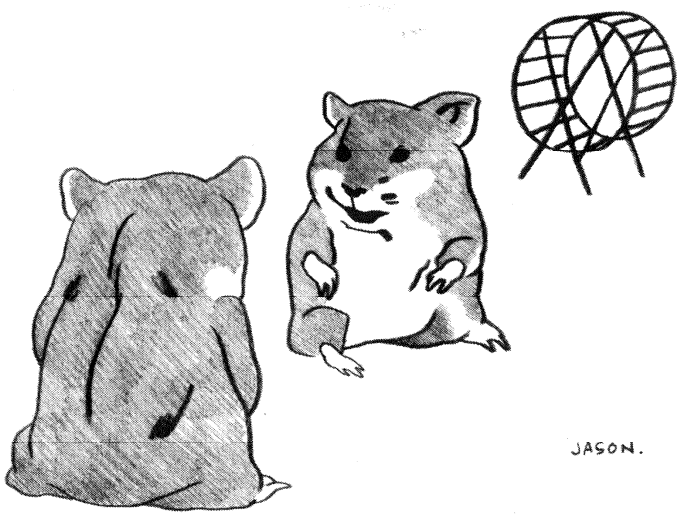
Antipsychotic and Mood Stabilizer Efficacy in Pediatric and Adult Patients with Bipolar I Mania

(Correll, C. et al; Bipolar Disorders 2010; 12; 116-141)

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



"I usually do two hours of cardio and then four more of cardio and then two more of cardio."

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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

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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)

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 all 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

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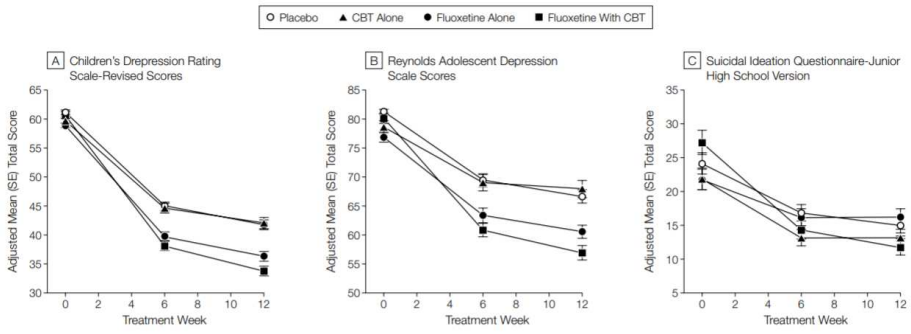
Adjusted Mean Mood (SE) Scale Scores for Participants in the TADS Study



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.

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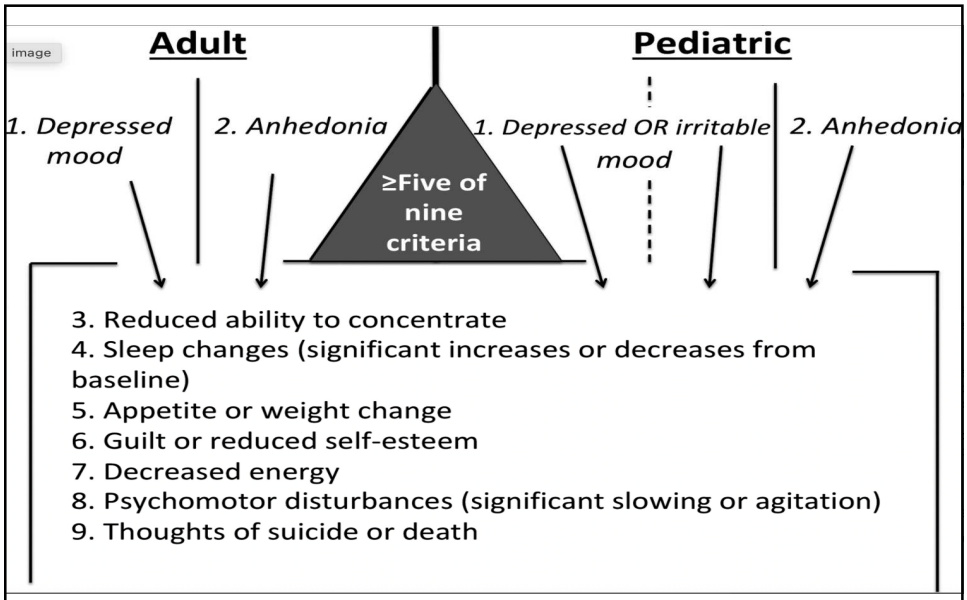
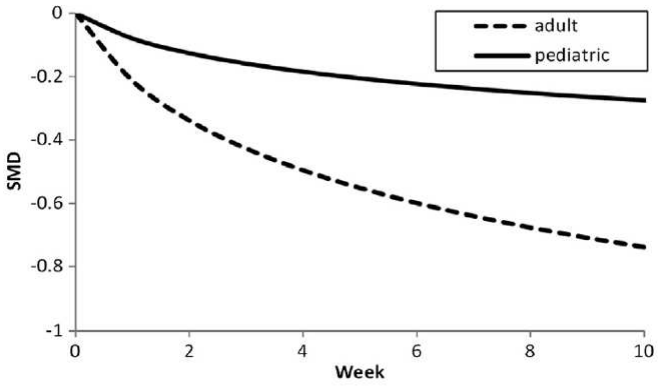


J Dwyer. Annual Research Review: Defining and treating pediatric treatment-resistant depression. 2020.

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. $p < .05$



Varigonda, L. Anjali. Systematic Review and Meta-Analysis: Early Treatment Responses of Selective Serotonin Reuptake Inhibitors in Pediatric Major Depressive Disorder. 2015.

Annual Research Review: Defining and Treating Pediatric Treatment-Resistant Depression

(Dwyer, J. Stringaris, A. Brent, D. Bloch, M. Journal of Child Psychology and Psychiatry; 2020: 61:3; 312-332)

- **Key Points:**
- 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 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.

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Table 1 First-line pharmacological treatments for adult depression and evidence of their effects in pediatric populations

	Pediatric				Adult				
	Starting dose (mg/day)	Typical dose range (mg/day)	Level of evidence in MDD	FDA indications	Starting dose (mg/day)	Typical dose range (mg/day)	Level of evidence in MDD	FDA indications	Half-life
Selective serotonin reuptake inhibitors									
Citalopram	10–20	20–40	C	–	20	40	A	MDD	20 hr
Escitalopram	10	10–20	A	MDD (12+)	10	10–20	A	MDD, GAD	27–32 hr
Fluoxetine	10–20	20–80	A	MDD (8+), OCD (7+)	20	20–80	A	MDD, OCD, PD	4–6 days
Fluvoxamine	25–50	50–300	C	OCD (8+)	100–300	100–300	A	OCD	16 hr
Paroxetine	10–20	20–60	C	–	10–20	40–60	A	MDD, OCD, PTSD, GAD, SAD, PD	21 hr
Sertraline	25–50	100–200	A	OCD (6+)	50	150–250	A	MDD, OCD, PTSD, SAD, PD	26 hr
Serotonin–norepinephrine reuptake inhibitors									
Venlafaxine	37.5	150–225	C	–	37.5–75	75–375	A	MDD, GAD, SAD, PD	10 hr
Duloxetine	30	40–60	C	GAD (7+)	20–60	20–80	A	MDD, GAD	12.5 hr
Desvenlafaxine	25	25–100	C	–	50	50–400	A	MDD	11 hr
Atypical antidepressants									
Bupropion	100	150–300	C	–	100–150	150–300	A	MDD	21 hr
Mirtazapine	7.5–15	15–45	C	–	15	15–45	A	MDD	20–40 hr
Vilazodone	5	10–20	C	–	10	10–40	A	MDD	25 hr
Vortioxetine	5	10–20	C	–	10	10–80	A	MDD	66 hr

J Dwyer. Annual Research Review: Defining and treating pediatric treatment-resistant depression. 2020.

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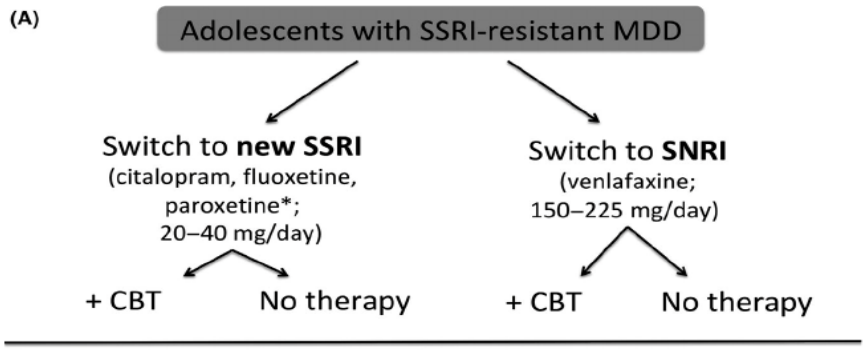

(B) TORDIA Take-home points:

(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

J Dwyer. Annual Research Review: Defining and treating pediatric treatment-resistant depression. 2020.

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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.

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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** (i.e 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

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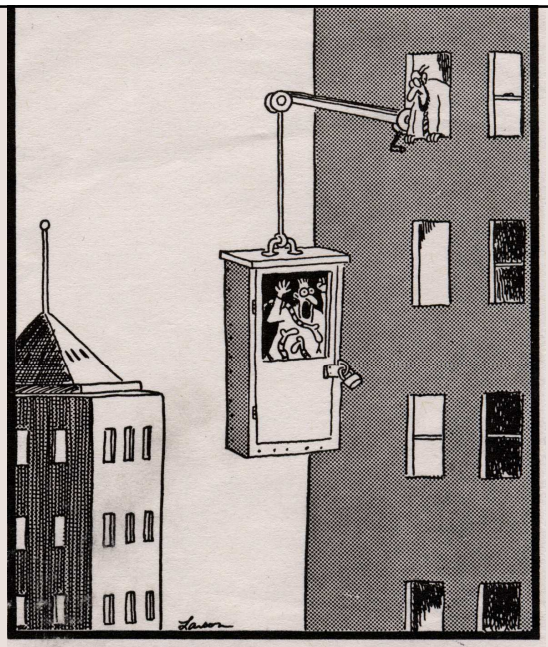

Professor Gallagher and his controversial technique of simultaneously confronting the fear of heights, snakes, and the dark

Child/Adolescent Anxiety Multimodal Study (CAMS)

(*Walkup J. et al. N Engl J Med. 2008 December 25; 359(26): 2753–2766. doi:10.1056/NEJMoa0804633)*

- **Design**: NIMH-funded randomized, controlled trial comparing sertraline, CBT, combination and placebo
- SAD, GAD and Social Phobia
- **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.

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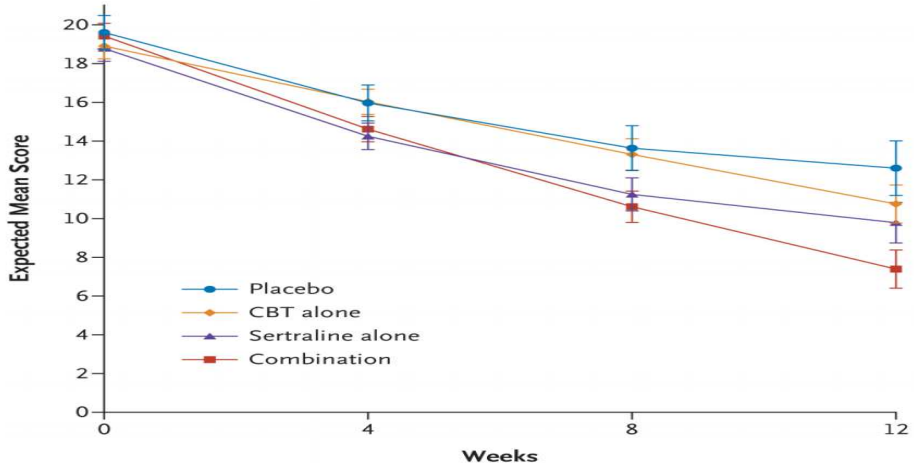

Figure 2. Scores on the Pediatric Anxiety Rating Scale during the 12-Week Study
Scores on the Pediatric Anxiety Rating Scale range from 0 to 30, with scores higher than 13 consistent with moderate levels of anxiety and a diagnosis of an anxiety disorder. The expected mean score is the mean of the sampling distribution of the mean. The I bars represent standard errors.

Walkup J. et al. N Engl J Med. 2008 December 25; 359(26): 2753–2766. doi:10.1056/NEJMoa0804633

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Escitalopram in Adolescents with Generalized Anxiety Disorder: A Double-Blind, Randomized, Placebo-Controlled Study

(Strawn JR, Mills JA, Schroeder H, Mossman SA et al. Escitalopram in Adolescents With Generalized Anxiety Disorder: A Double-Blind, Randomized, Placebo-Controlled Study. J Clin Psychiatry. 2020 Aug 25;81(5):20m13396. doi: 10.4088/JCP.20m13396. PMID: 32857933; PMCID: PMC7504974).

- **Background:** SSRIs are commonly used to treat pediatric anxiety disorders, including generalized anxiety disorder (GAD); however, their efficacy and tolerability are difficult to predict.
- We evaluated the efficacy and tolerability of escitalopram in adolescents with GAD and the impact of CYP2C19 phenotype on escitalopram pharmacokinetics from February 2015 through November 2018.
- **Methods:** Patients were treated with escitalopram (forced titration to 15 mg/day, then flexible titration to 20 mg/day) (n=26, mean age: 14.8±1.7 years) or placebo (n=25 mean age: 14.9±1.6 years) for 8 weeks.
- Outcomes were the change in the Pediatric Anxiety Rating Scale (PARS) score and Clinical Global Impressions (CGI) scales. Plasma escitalopram and des-methylescitalopram AUC0-24 and CMAX were determined and compared across CYP2C19 phenotypes.
- **Results:** Escitalopram was superior to placebo for baseline-to-endpoint change in PARS (–8.65±1.2 vs. –3.52±1.1, p<0.001) and CGI
- Increasing CYP2C19 metabolism was associated with decreases in escitalopram CMAX and AUC0-24 (p<0.05). Vital signs, QTc and adverse events were similar in patients who received escitalopram and placebo.
- **Conclusions:** Escitalopram reduces anxiety symptoms and CYP2C19 phenotype influences the trajectory and magnitude of improvement. Variation in CYP2C19 metabolism accounts for significant differences in escitalopram pharmacokinetics.

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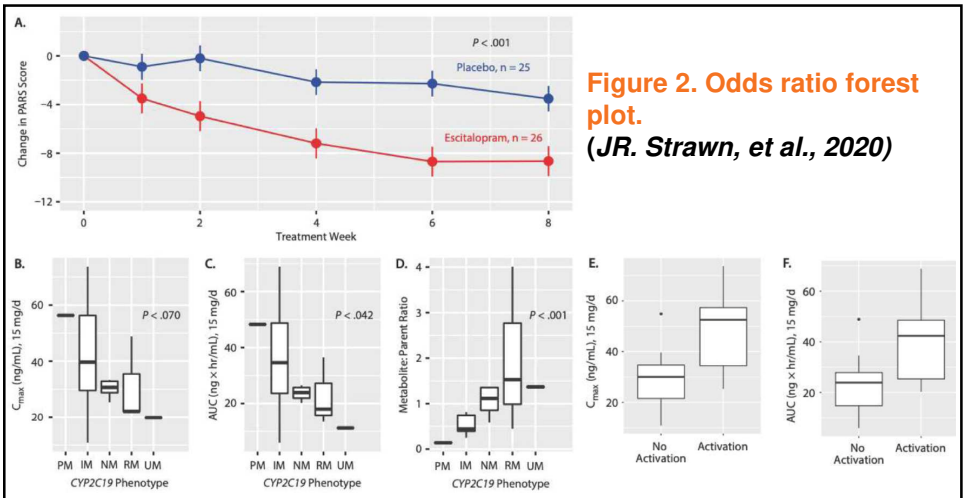

Figure 2. Odds ratio forest plot.
(*JR. Strawn, et al., 2020)*

Figure 2:
(A) Change Over Time in PARS Score for Escitalopram Versus Placebo[a]; Change From Baseline to Endpoint by *CYP2C19* Phenotype in (B) Maximum Concentration (C_{max}), (C) Area Under the Curve (AUC), and (D) Metabolite:Parent Drug Ratio[b]; and Difference in (E) C_{max} and (F) AUC Between Patients With and Without Activation Symptoms
[a]Values shown as mean ±SD.
[b]Boxplots for parts B, C, and D show median (IQR) and minimum and maximum values.
[c]Boxplots for parts E and F show median (IQR) and minimum and maximum values and outliers.
Abbreviations: *CYP2C19*=cytochrome P450 2C19, IM=intermediate metabolizer, IQR=interquartile range, NM=normal metabolizer, PM=poormetabolizer, RM=rapid metabolizer, UR=ultrarapaid metabolizer.

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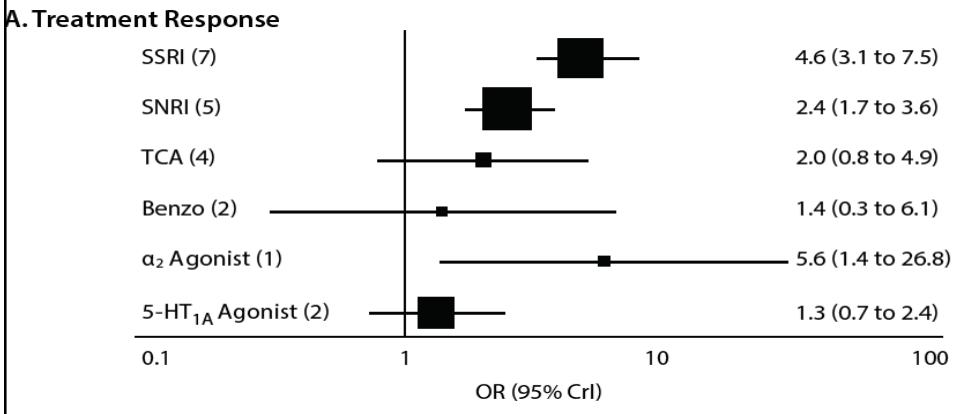
Treatment of Pediatric Anxiety Disorders: Serotonin Reuptake Inhibitors: FDA Approvals

- 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

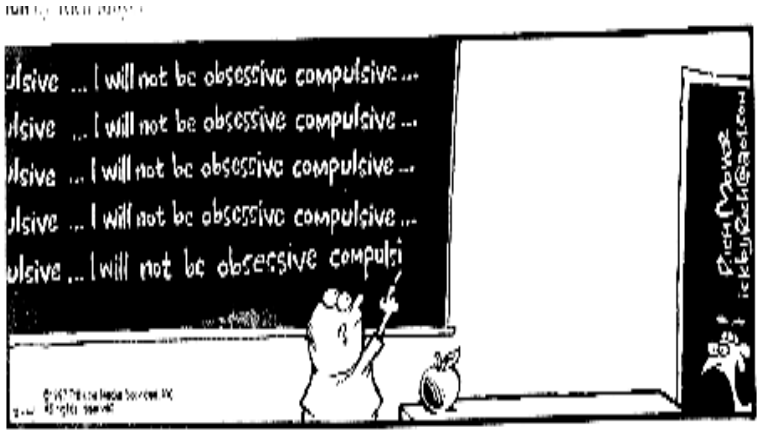
Figure 2. Forest Plot of Medication Class Efficacy Relative to Placebo for Treatment Response (A) and Anxiety Symptom Improvement (B) and Funnel Plots for Treatment Response (C), Anxiety Symptom Improvement (D), All-Cause Discontinuation (E), and Discontinuation Due to Adverse Events (F)



Dobson, T. Eric. Efficacy and Tolerability of Pharmacotherapy for Pediatric Anxiety Disorders: A Network Meta-Analysis. 2019.

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.



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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

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Developmental Considerations in Obsessive Compulsive Disorder: Comparing Pediatric and Adult-Onset Cases

(Geller DA, Homayoun S, Johnson G. Developmental Considerations in Obsessive Compulsive Disorder: Comparing Pediatric and Adult-Onset Cases. Front Psychiatry. 2021 Jun 14;12:678538. doi: 10.3389/fpsyt.2021.678538. PMID: 34248714; PMCID: PMC8269156).

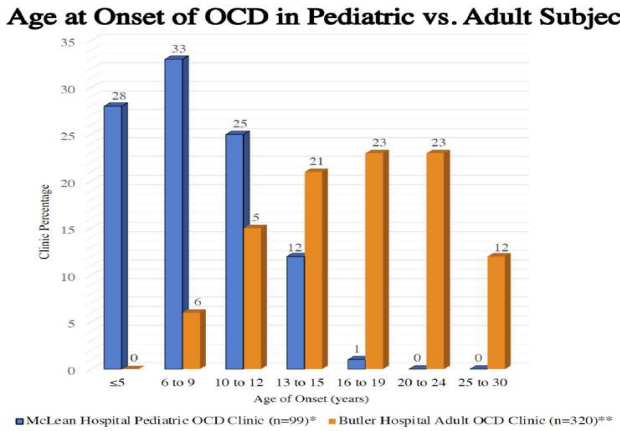

FIGURE 1 | A Bimodal distribution of incidence of OCD across the lifespan. *Geller et al. (22). **Rasmuseen et al. (23).

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Developmental Considerations in Obsessive Compulsive Disorder: Comparing Pediatric and Adult-Onset Cases

(Geller DA, Homayoun S, Johnson G. Developmental Considerations in Obsessive Compulsive Disorder: Comparing Pediatric and Adult-Onset Cases. Front Psychiatry. 2021 Jun 14;12:678538. doi: 10.3389/fpsyt.2021.678538. PMID: 34248714; PMCID: PMC8269156).

TABLE 1 | DSM5 OCD specifiers relevant to pediatric OCD.

Specify if:	With good or fair insight: The individual recognizes that obsessive-compulsive disorder beliefs are definitely or probably not true or that they may or may not be true.
	With poor insight: The individual thinks obsessive-compulsive disorder beliefs are probably true.
	With absent insight/delusional beliefs: The individual is completely convinced that obsessive-compulsive disorder beliefs are true.
Specify if:	Tic-related: The individual has a current or past history of a tic disorder.

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Overview of Treatment: Pediatric OCD
First Line: Cognitive Behavioral Therapy

Psycho-education
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.

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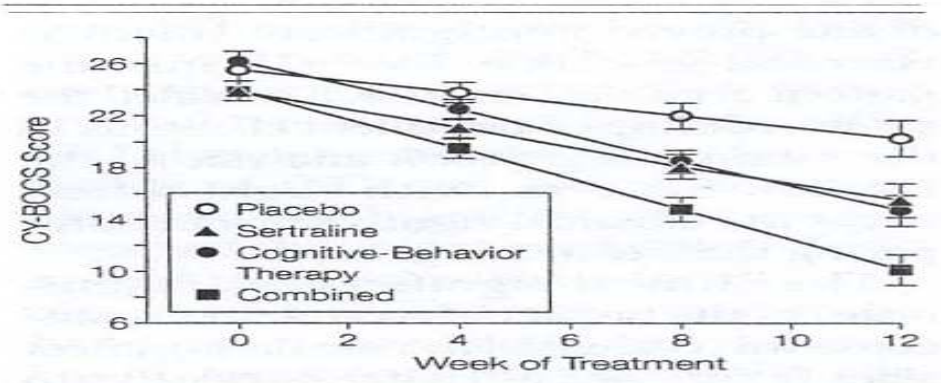
Weekly Adjusted Intent-to-Treat CY-BOCS Score, by Treatment Group



Range of possible scores for the Children's Yale-Brown Obsessive-Complusive 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

	Empirical Support			
Medication	**Child**	**Adult**	**Starting Dose (mg)**	**Usual Dose Range (mg/day)**
Clomipramine	A	A	25-50	100-250
Fluoxetine	A	A	5-20	10-60
Sertraline	A	A	25-50	50-250
Fluvoxamine	A	A	25-50	50-350
Paroxetine	B	A	5-10	10-60
Citalopram	B	A	5-10	20-60
Escitalopram*	B	A	5-10	10-20

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

Scahill et al. 2006

Practical Guidelines for Pediatric OCD Pharmacotherapy

- 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
- Monitor potential 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:

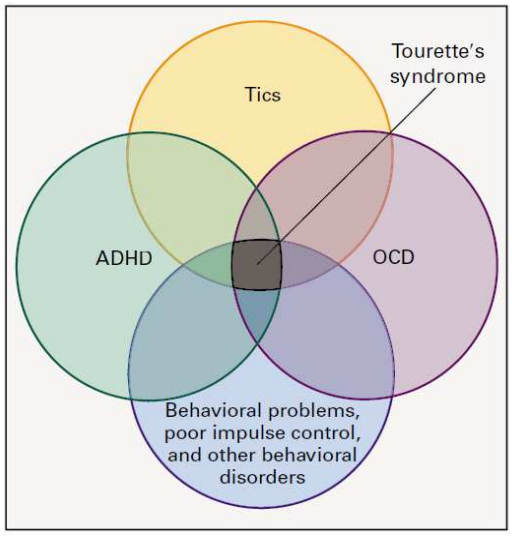
Single or multiple motor tics and/or vocal tics have been present during the illness, but **not both** motor and vocal.

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.



Jankovic J.NEJM; 2001.

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.

Daily Doses of Frequently Prescribed Tic Medications

(Egolf, A. Coffey, B. Current Pharmacotherapeutic Approaches to the Treatment of Tourette Syndrome: Drugs Today; 2014 Feb; 50 (2):159-79. doi: 10.1358/dot.2014.50.2.2097801). *off label

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

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Ecopipam for Tourette Syndrome: A Randomized Trial

(*Gilbert DL, Dubow JS, Cunniff TM, et al Ecopipam for Tourette Syndrome: A Randomized Trial. Pediatrics. 2023 Feb 1;151(2):e2022059574. doi: 10.1542/peds.2022-059574. PMID: 36628546.*)

TABLE 1 Baseline Characteristics (Safety Population)

	Placebo (n = 77)	Ecopipam (n = 76)
Age, years, mean ± SD	12.6 ± 2.6	12.6 ± 2.8
6 to 11 y, n (%)	26 (33.8)	27 (35.5)
12 to <18 y, n (%)	51 (66.2)	49 (64.5)
Male, n (%)	53 (68.8)	59 (77.6)
Race, n (%)		
White	72 (93.5)	66 (86.8)
Black/African American	3 (3.9)	6 (7.9)
Asian	2 (2.6)	1 (1.3)
Other	0	3 (4.0)
Wt, kg, mean ± SD	56.1 ± 21.5	58.2 ± 25.8
North America, n (%)	60 (77.9)	64 (84.2)
Europe, n (%)	17 (22.1)	12 (15.8)
Medical history, n (%)		
Attention-deficit/hyperactivity disorder	30 (39.0)	39 (51.3)
Depression	5 (6.5)	4 (5.3)
Obsessive-compulsive disorder	11 (14.3)	14 (19.4)
Medication use, n (%)		
Antipsychotics (previous)	20 (26.0)	20 (26.3)
Antidepressants (concomitant)	19 (24.7)	23 (30.1)
Baseline tic scores mean ± SD		
YGTSS-TTS	34.7 ± 5.6	34.6 ± 6.3
YGTSS-GS	66.4 ± 11.6	68.0 ± 13.0
CGI-TS	4.8 ± 0.68	4.8 ± 0.94

SD, standard deviation.

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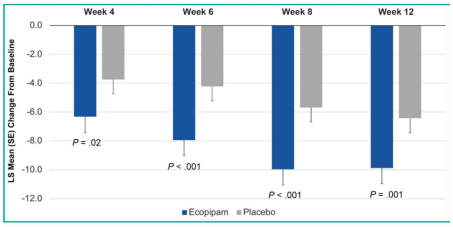
FIGURE 2

(A) YGTSS-TTS LS mean (SE) change from baseline to week 4, 6, 8 and 12 and (B) YGTSS-GS LS mean (SE) change from baseline to week 4, 6, 8, and 12. *P* values from MMRM analysis.

A



B

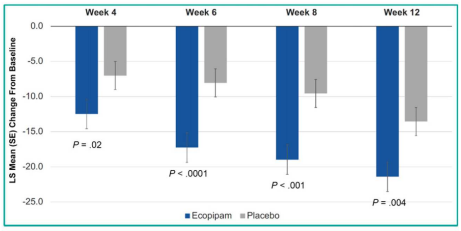


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TABLE 2 Incidence of Treatment-Emergent AEs (At Least 5% Greater Incidence With Ecopipam, Safety Population)

	Number (%) of Subjects	
	Placebo (n = 77)	Ecopipam (n = 76)
Headache	7 (9.1)	12 (15.8)
Insomnia	2 (2.6)	10 (13.1)
Fatigue	0	6 (7.9)
Somnolence	2 (2.6)	6 (7.9)
Anxiety	0	4 (5.3)
Nausea	1 (1.3)	4 (5.3)
Restlessness	0	4 (5.3)
Any AE	38 (49.4)	47 (61.8)
Treatment-related AE	16 (20.8)	26 (34.2)
AE leading to withdrawal	1 (1.3)[a]	4 (5.3)[b]
Serious AE	1 (1.3)[c]	2 (2.6)[d]

Treatment-related AEs were AEs with relationship to treatment as "Possibly Related" or "Probably Related."

[a] Suicidal ideation based on C-SSRS defined as nonspecific suicidal thoughts or active suicidal ideation without intent to act.

[b] 4 subjects with nausea, anxiety, depressed mood, self-injurious ideation, suicidal ideation, tic.

[c] Suicidal ideation.

[d] Coronavirus disease 2019 infection, vomiting.

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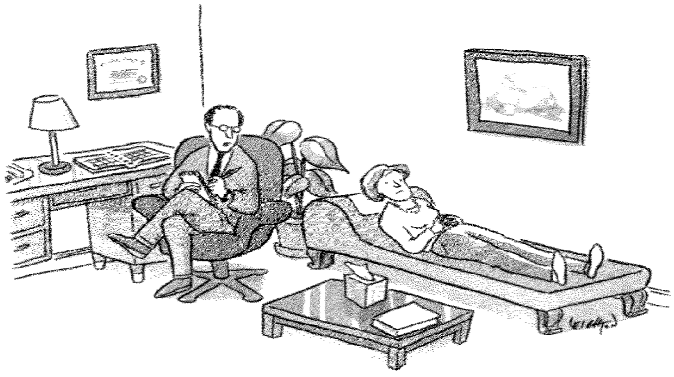

"If you're happy and you know it, stick with your dosage."

THURSDAY
SEPTEMBER 25

Summary: Child and Adolescent Psychopharmacology

- Psychiatric disorders are **highly prevalent** in youth.
- Psychotropic medication, while effective, has a range of potentially concerning adverse effects. **A safer profile emerged for escitalopram and fluoxetine among antidepressants, lurasidone for antipsychotics, methylphenidate among anti-ADHD medications, and lithium among mood stabilizers.**
- **ADHD** generally persists; hyperactive-impulsive symptoms attenuate over time. Functional outcomes are highly impacted; medication improves outcomes.
- **Stimulants** are among the most effective medications in medicine and are generally safe. Several **new stimulant delivery systems** cover a wide range of options.
- **Non-stimulants** are also effective for ADHD.
- **Several SGAs** in youth are approved for treatment of early onset schizophrenia and bipolar disorder**.**
- **DMDD** diagnosis is rising relative to pediatric bipolar disorder, but there has been no significant reduction in antipsychotic use.
- **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 a less robust response than adults.
- **SSRIs** are effective 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**.
- A recent clinical trial of **ecopipam** showed promising results.
- Tune in next year!