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PSYCHIATRY ACADEMY

Pediatric Anxiety Disorders
Child and Adolescent Psychopharmacology

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Disclosures

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

- American Academy of Child and Adolescent Psychiatry: Honoraria
- Emalex: Research Support
- Harvard Medical School /Psychiatry Academy: Honoraria
- New Venture Fund: Research Support
- 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; TAA-CDC Partnership

Off-label indications will be discussed

Pediatric Anxiety Disorders

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Learning Objectives:

- At the end of this session, the participant should be able to:
- Review **clinical phenomenology** of pediatric anxiety disorders
- Review **helpful rating instruments** for evaluation of pediatric anxiety disorders
- Become familiar with recent studies of **pharmacological treatment of pediatric anxiety** disorders
- **Apply updates** on pharmacological treatment of pediatric anxiety disorders to **clinical practice**

Lifetime Prevalence of Mental Disorders in US Adolescents *(Merikangas, K. et al JAACAP; 2010; 49 (10); 980-989)*

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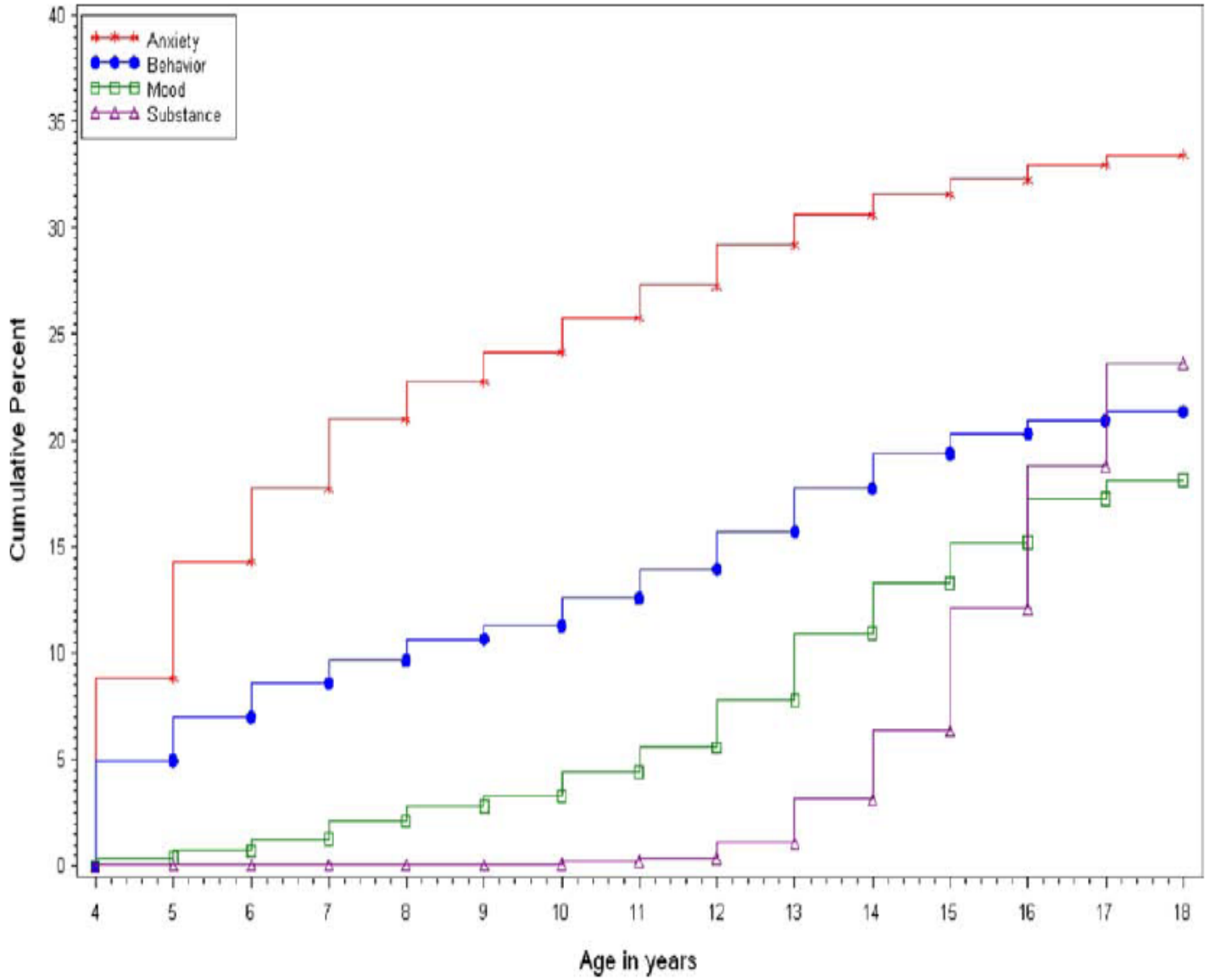
- **Design:** National Comorbidity Survey-Adolescent Supplement
- Face to face survey of 10, 123 adolescents, age 13-18, in US
- **Results: Anxiety disorders (32%),** Behavior Disorders (19%), Mood Disorders (14%) and Substance Use Disorders (11%).
- Overall prevalence of disorders with severe impairment 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).



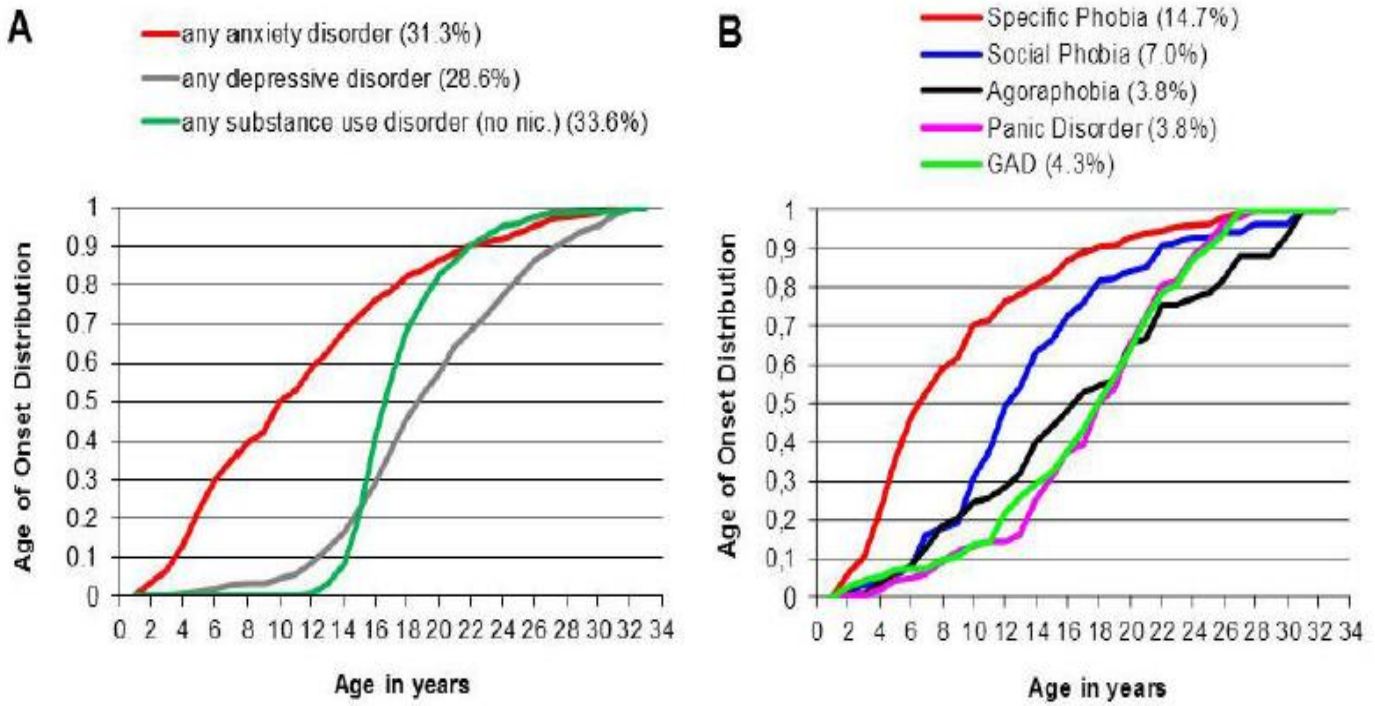


FIGURE 1. The age of onset distribution of (A) anxiety, depressive and substance use disorders and (B) specific anxiety disorders at age 33, and estimated cumulative incidence rates at age 33 (in parenthesis)

Data from the Early Developmental Stages of Psychopathology (EDSP) Study. *Adapted from [8].*

Wehry et al. (2015)

Pediatric Anxiety Disorders: Prevalence and Course

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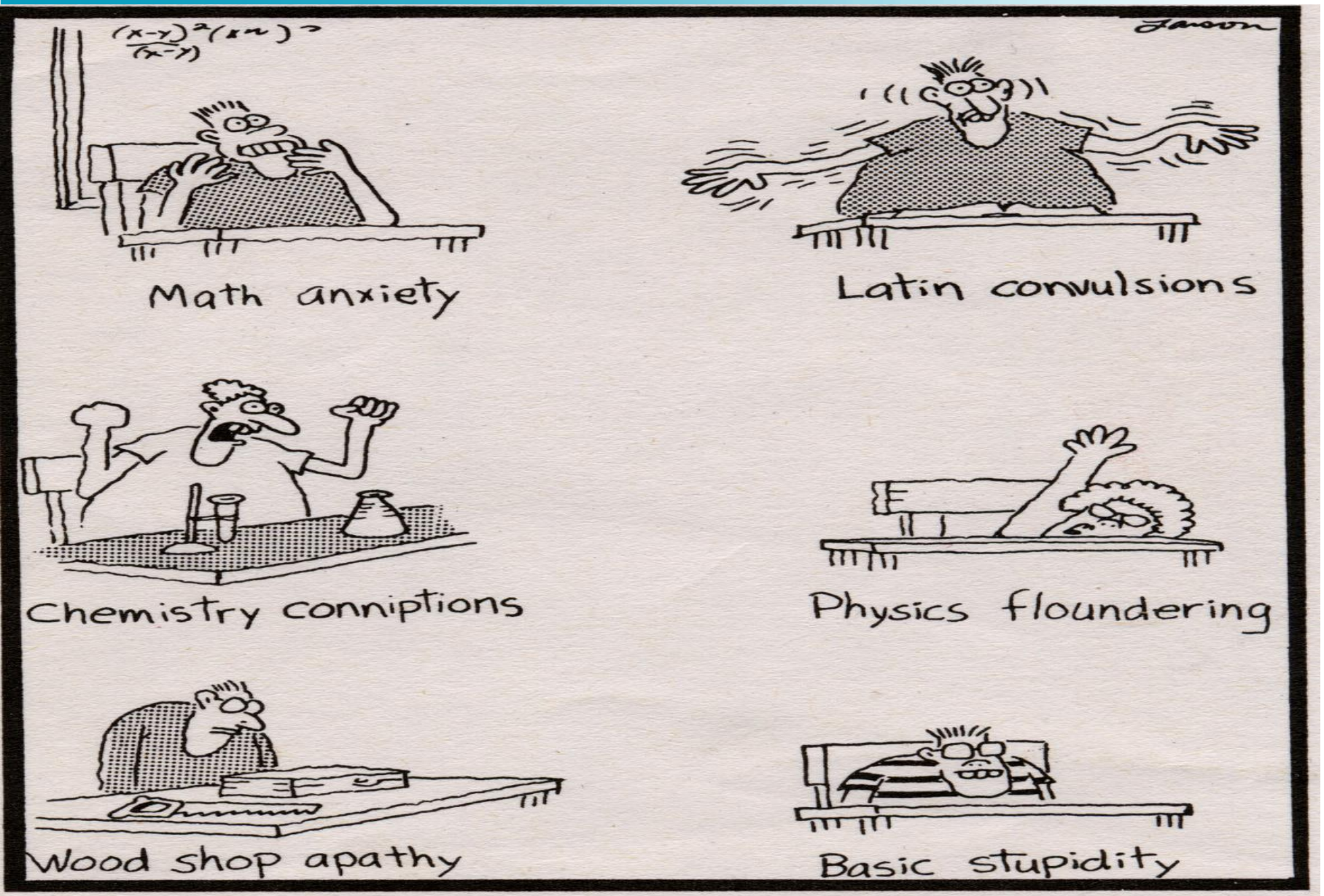
- **Anxiety disorders** are common (6-20%) in children and adolescents.
- Lifetime prevalence (20-30%) is high.
- Anxiety disorders are frequently **comorbid with one another and with mood disorders** in children and adolescents. Recurrences are common.
- Median odds ratios in meta-analysis of 15 population studies for association between anxiety disorder: **ADHD 3.0, Conduct Disorder 3.1 and Major Depressive Disorder 8.2**. (Angold et al 1999)
- Course is often **chronic with waxing and waning** symptoms: both **homotypic** (predicts same disorder) and **heterotypic** (predicts different disorder) continuity.
- Common "**negative valence systems**"
- Examples: Separation Anxiety Disorder predicts Panic Disorder and Major Depression
- Selective mutism predicts Social Anxiety Disorder in adolescence/adulthood. (AACAP Practice Parameters, 2020)



Classroom afflictions

Diagnosis: Pediatric Anxiety Disorders: Common Symptoms

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- Excessive need for **reassurance**
- **Avoidance of or significant distress** with age appropriate interests and activities
- **Physical complaints**: headaches, stomach aches, body pains, change in appetite
- **Sleep disturbance**: initial, middle or late insomnia; inability to sleep alone or repeated visits to parents' bedroom
- Difficulty with **concentration and attention**

Diagnosis: Pediatric Anxiety Disorders: Diagnostic Instruments/Rating Scales

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- **Structured/Semi-Structured Diagnostic Interviews:**

- Schedule for Affective Disorders and Schizophrenia (KSADS-PL; Kaufman et al, 1997))
- Anxiety Disorders Interview Schedule (ADIS, Silverman and Albano)
- Diagnostic Interview Schedule for Children (DISC)

Diagnosis: Pediatric Anxiety Disorders: Diagnostic Instruments/Rating Scales

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- **Self Report Instruments**:
- Multidimensional Anxiety Scale for Children (MASC) (DSM based; John March, 1997)
- SCARED: Self Report for Childhood Anxiety Related Disorders
- **Parent/Teacher Ratings:**
- Achenbach Child Behavior Checklist (CBCL)
- **Clinician Ratings:**
- Pediatric Anxiety Rating Scale (PARS)

Cognitive Behavioral Therapy, Sertraline, or a Combination in Childhood Anxiety (CAMS)

(Walkup, J. N Engl J Med. 2008; 359(26): 2753–2766)

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- **Design:** NIMH-funded randomized, controlled trial comparing sertraline, CBT, combination and placebo SAD, GAD and Social Phobia
  - N=488
  - Mean age: 10-11
  - 12 weeks acute phase
  - 6 month follow-up
- **Results:**
  - Mean dose ~140 mg/day
  - Response: Combination 81%
  - CBT 60%
  - Sertraline 56%
  - PBO 24%
- **Conclusion**: Combination was most effective treatment, and both CBT and medication were more effective than placebo.

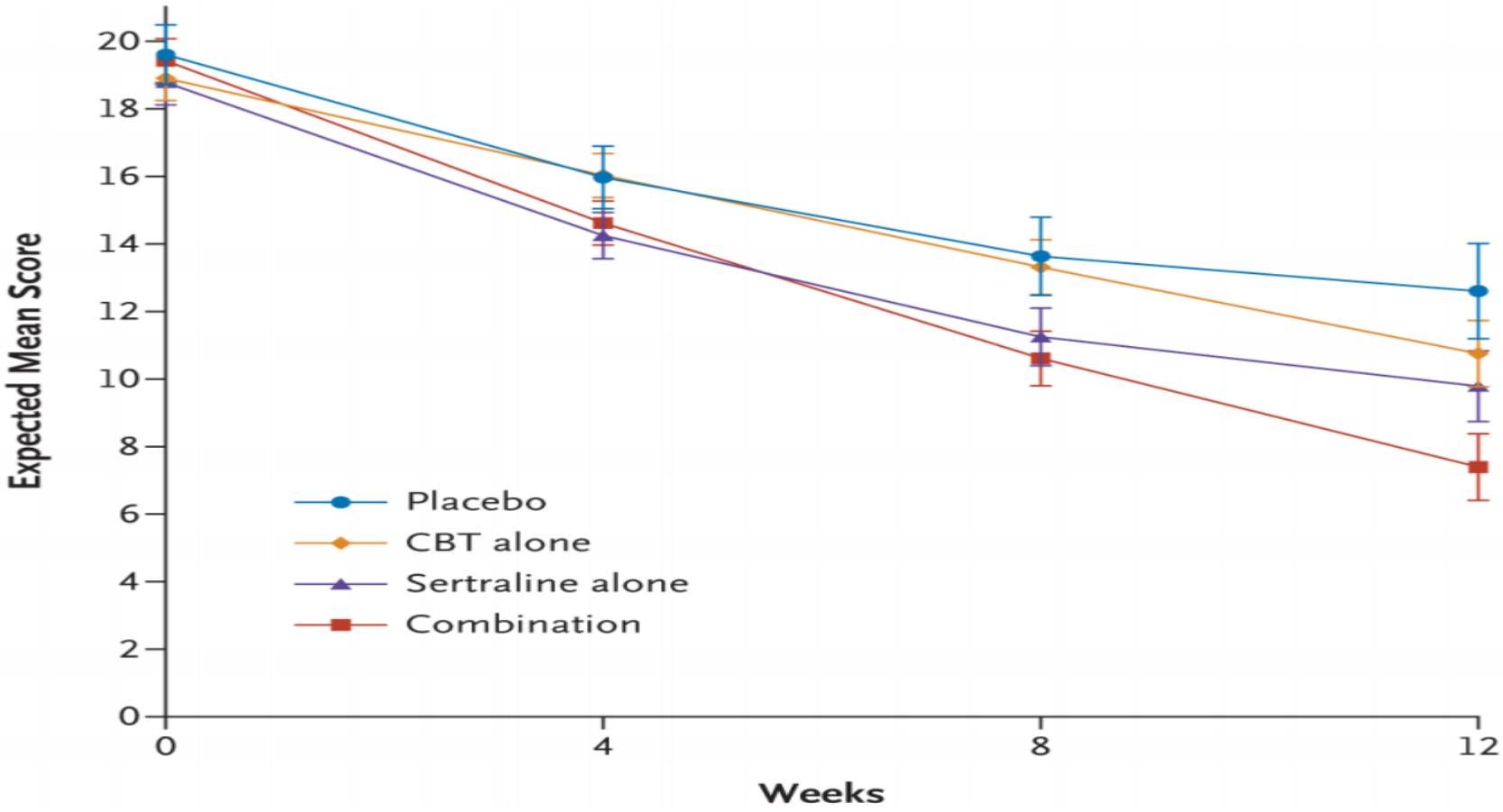

Figure 2. Scores on the Pediatric Anxiety Rating Scale during the 12-Week Study
Scores on the Pediatric Anxiety Rating Scale range from 0 to 30, with scores higher than 13 consistent with moderate levels of anxiety and a diagnosis of an anxiety disorder. The expected mean score is the mean of the sampling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

Cognitive Behavioral Therapy, Sertraline, or a Combination in Childhood Anxiety *(Walkup, J. N Engl J Med. 2008; 359(26): 2753–2766. doi:10.1056/NEJMoa0804633).*

Pediatric Anxiety Disorders: Treatment Overview

(Clinical Practice Guideline for the Assessment and Treatment of Children and Adolescents with Anxiety Disorders; JAACAP, 2020; 59 (10); 1107-1124)

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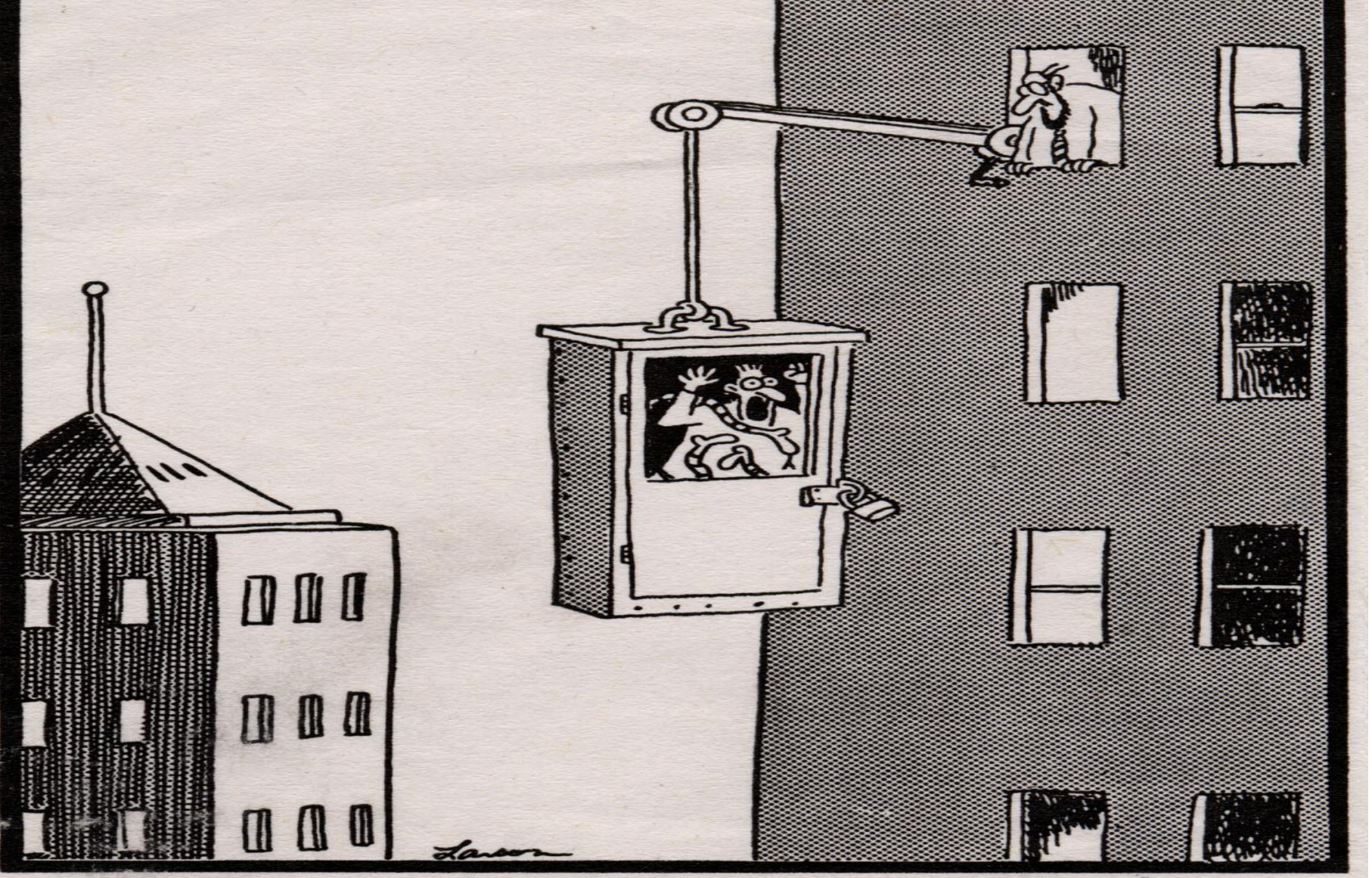
- Developed treatment statements from AHRQ/Mayo Systematic Review based on **strength of the evidence (**SOE)
- SOE: high, moderate or low
- 1) AACAP recommends **CBT** be offered to patients age 6-18 with social anxiety, generalized anxiety, separation anxiety, specific phobia or panic disorder.
- 2) AACAP recommends that **SSRIs** be offered to patients age 6-18 with social anxiety, generalized anxiety, separation anxiety or panic disorder.
- 3) AACAP suggests that **combination treatment (CBT and an SSRI)** could be offered over CBT alone or an SSRI alone to patients age 6-18 with social anxiety, generalized anxiety, separation anxiety, or panic disorder.
- 4) AACAP suggests that **serotonin norepinephrine reuptake inhibitors (SNRIs)** could be offered to patients age 6-18 with social anxiety, generalized anxiety, separation anxiety, or panic disorder.



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

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Treatment of Pediatric Anxiety Disorders: Applications to Clinical Practice

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Comprehensive evaluation is essential; information must be obtained from parents, child, and teacher

Consider likelihood of **high comorbidity**

Psychoeducation is the first step

Mild-moderate symptoms are usually responsive **to cognitive behavioral therapy**

Pharmacotherapy: SSRIs are the treatment of choice

SNRIs and alpha 2 agonists may be helpful

Limited data for benzodiazepines

Off label prescribing may be necessary

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

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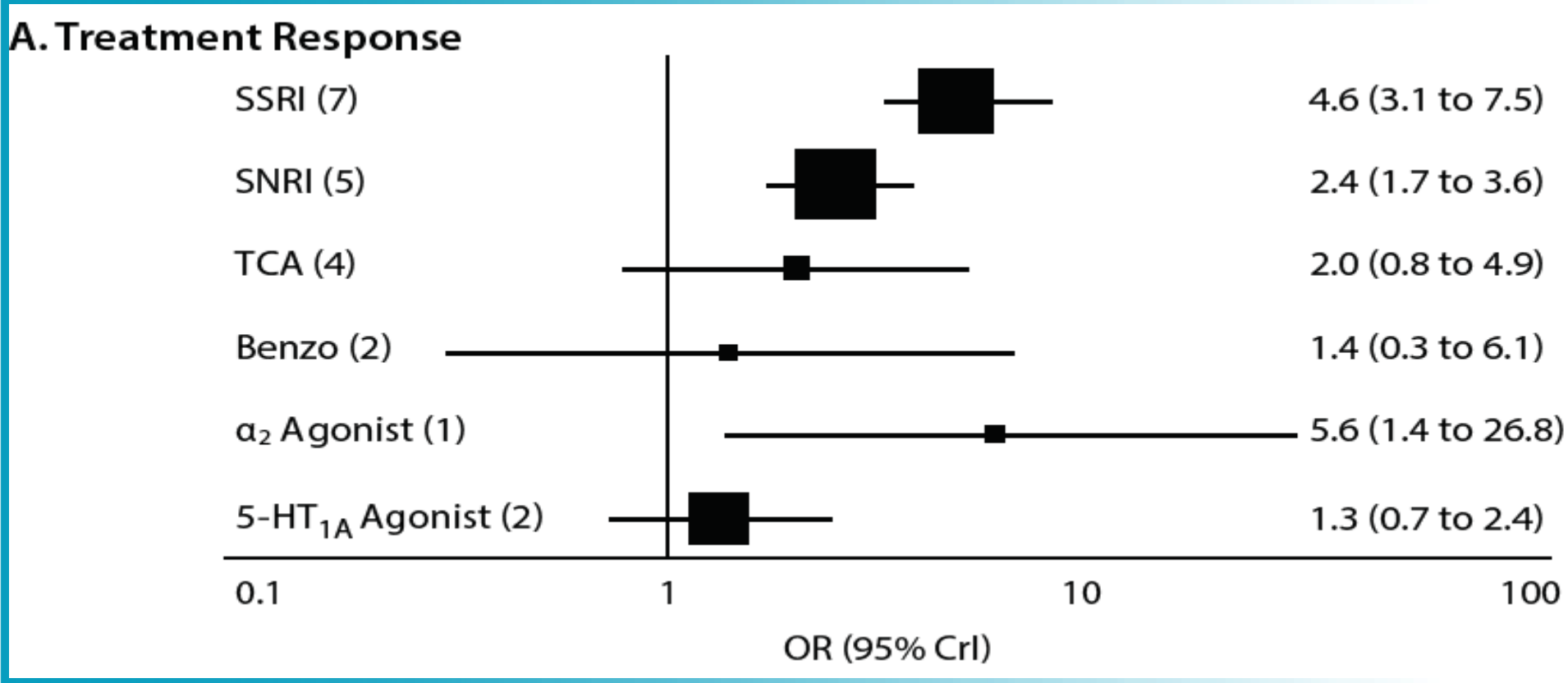
- Clomipramine - FDA approved > age 10 OCD
- Fluvoxamine - FDA approved > age 8 OCD
- Sertraline - FDA approved > age 6 OCD
- Escitalopram – FDA approved > age 12 for depression
- Fluoxetine – effective for OCD; FDA approved MDD > age 7
- Paroxetine – effective for OCD and Social Phobia
- Citalopram – No controlled trials in children

TABLE 7. Medications with evidence-based efficacy and FDA approval for treatment of anxiety disorders in youth

	Available forms	Generic available	Daily therapeutic dose guidelines		
			<40 lbs	40-90 lbs	>90 lbs
Selective serotonergic reuptake inhibitors					
Fluoxetine[b] (Prozac)	Solution; 10, 20, 40 Pulvules; 90 mg Prozac weekly	Yes	2-6 mg	6-20 mg	5-60 mg
Sertraline[b] (Zoloft)	25, 50, 100 mg tablets	Yes	12.5-25 mg	12.5-100 mg	12.5-200 mg
Paroxetine (Paxil)	10, 20, 30, 40 mg tablets CR 12.5, 25, 37.5 mg tablets; solution	Yes	2-5 mg	5-30 mg	5-60 mg
Fluvoxamine[b] (Luvox)	25, 50, 100 mg tablets	Yes	12.5-25 mg	25-100 mg	25-300 mg
Other antidepressants					
Venlafaxine (Effexor)	Extended release (XR) 37.5, 50, 75, 100 mg tablets; 37.5, 75, 150 mg capsules	No Yes	37.5 mg 25-50 mg	37.5-112.5 mg 25-150 mg	37.5-225 mg 25-300 mg
Clomipramine[b] (Anafranil)	25, 50, 75 mg capsules	Yes	1-5 mg/kg/day	1-5 mg/kg/day	1-5 mg/kg/day, Not to exceed 300 mg/day
Imipramine (Tofranil)	10, 25, 50 mg tablets; 75, 100, 125, 150 mg capsules	Yes	1-5 mg/kg/day	1-5 mg/kg/day	1-5 mg/kg/day, Not to exceed 300 mg/day

Rockhill, C. et al. (2010)

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.

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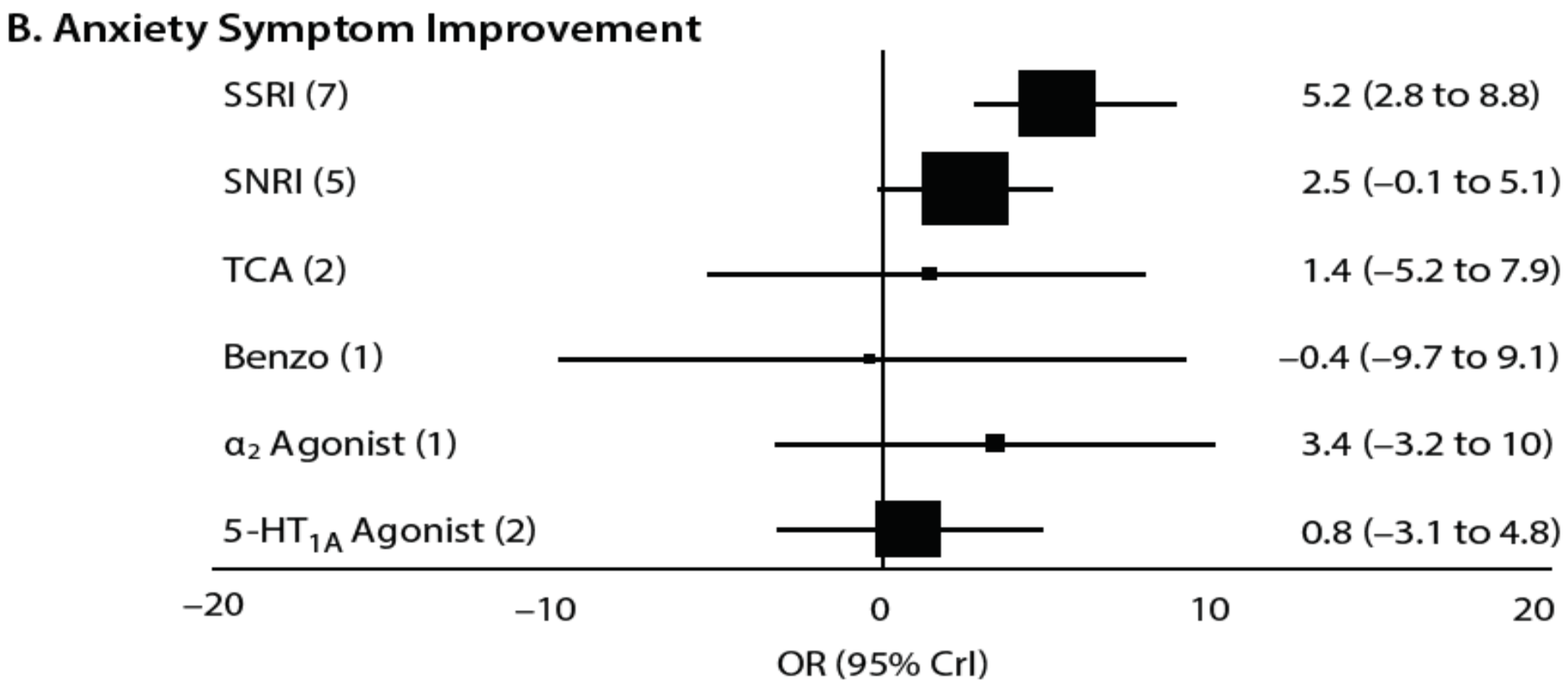

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Impact of Antidepressant Dose and Class on Treatment Response in Pediatric Anxiety Disorders: A Meta-Analysis

(Strawn, J. et al; JAACAP; 2018; 57 (4); 235-244)

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- **Objective:** To determine trajectory and magnitude of antidepressant response and effect of antidepressant class and dose on symptomatic improvement in pediatric anxiety disorders.
- **Method:** Weekly symptom severity data were extracted from RCTs of SSRIs and SNRIs in pediatric anxiety disorders.
- Change in symptom severity was evaluated as a function of time, class, and for SSRIs, standardized dose.
- **Results:** Data from 9 trials (SSRIs=5; SNRIs=4) for 7 medications in 1,673 youth were included.
- Statistically, but not clinically, **significant treatment effects emerged within 2 weeks of beginning treatment, and by week 6, clinically significant differences emerged.**

Impact of Antidepressant Dose and Class on Treatment Response in Pediatric Anxiety Disorders: A Meta-Analysis

(Strawn, J. et al; JAACAP; 2018; 57 (4); 235-244)

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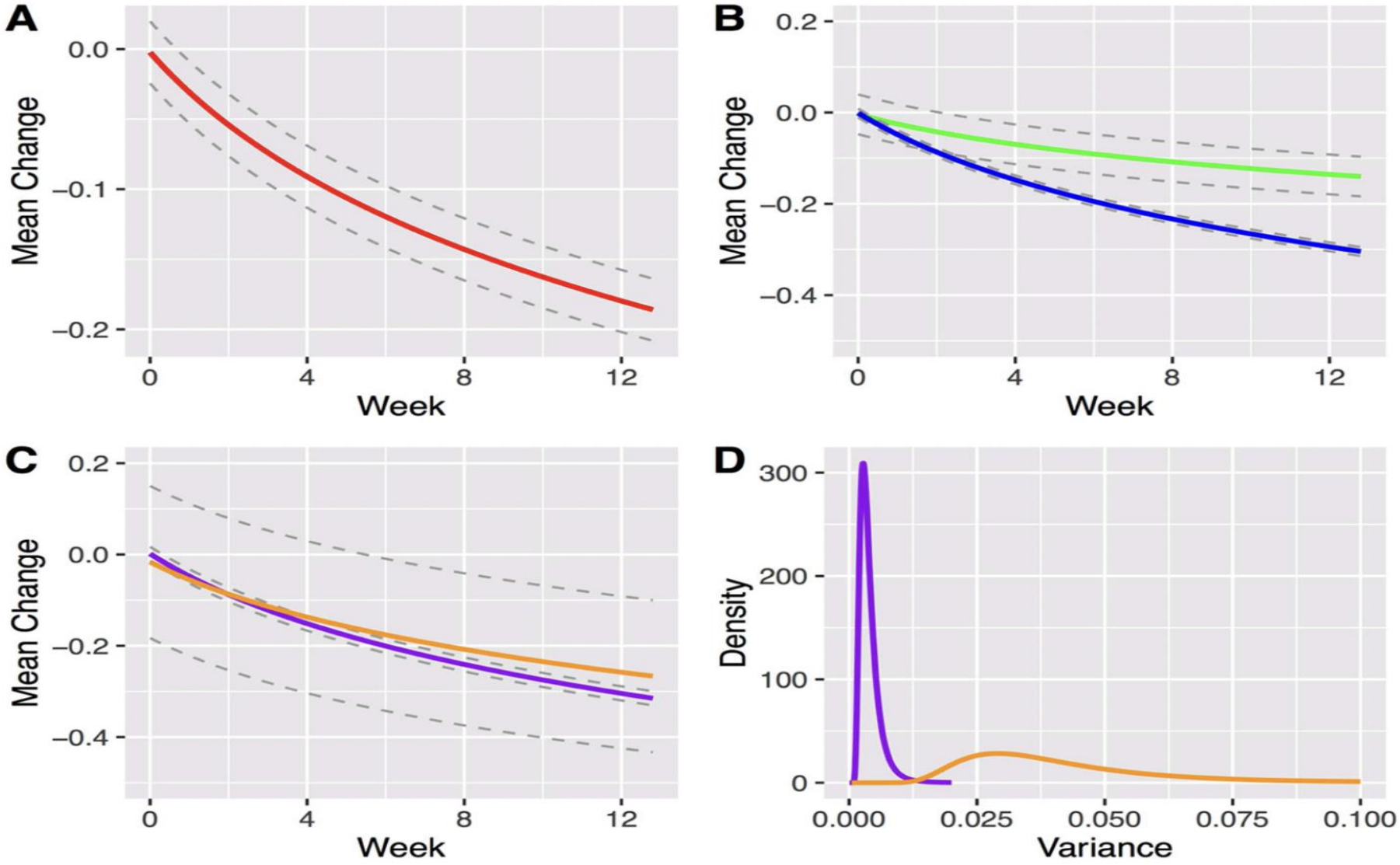
- **Results:** Compared to SNRIs, SSRIs resulted in **significantly greater improvement by the second week of treatment** ($p=0.0268$) and this advantage remained statistically significant through week 12 ($p<0.03$).
- Improvement occurred **earlier with high dose SSRI** treatment (week 2, $p=0.002$) compared to low dose treatment (week 10, $p=0.025$), but SSRI dose did not impact overall response trajectory (weeks 1-2, $p>0.18$)
- **Conclusion:** In pediatric patients with GAD, SAD, and/or social anxiety disorder, antidepressant related improvement occurs early in the course of treatment.
- SSRIs are associated with **more rapid and greater improvement** compared to SNRIs.



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Strawn J.. The Impact of Antidepressant Dose and Class on Treatment Response in Pediatric Anxiety Disorders: A Meta-Analysis. 2018.

Green lines=SNRIs. Blue lines=SSRIs. Purple lines=high dose SSRI. Orange lines=low dose SSRIs.

Extended Release Guanfacine in Pediatric Anxiety Disorders: A Pilot, Randomized Placebo Controlled Trial

(Strawn, J. et al; JCAP; 2017; (27);1; 29-37)

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- **Method:** Feasibility study to evaluate safety and tolerability of extended release guanfacine (GXR).
- Children and adolescents age 6-17 years with primary diagnosis of GAD, SAD and/or social anxiety disorder were treated with flexibly dosed GXR, 1-6 mg daily (N=62) or placebo (N=21) for 12 weeks.
- **Results:** GXR was safe and well tolerated. Treatment emergent adverse effects (TEAEs) were similar in both GXR and placebo groups.
- TEAEs were consistent with known safety profile, including headache, somnolence/fatigue, abdominal pain, and dizziness.
- No differences were noted between GXR and placebo in PARS and SCARED scores; at endpoint a higher proportion of subjects on GXR demonstrated CGI-I <2 (54.2% vs.31.6%).
- **Conclusion:** GXR was safe and well tolerated in pediatric patients with GAD, SAD and/or social anxiety disorder.

Table 1. Demographic and Baseline Characteristics of Subjects

Characteristic	*Placebo (n=21)*	*GXR (n=62)*	*Total (n=83)*
Mean age, years ± SD	11.8 ± 3.46	11.7 ± 3.39	11.7 ± 3.38
Age group,[a] *n* (%)			
6–12 years	12 (57.1)	38 (61.3)	50 (60.2)
13–17 years	9 (42.9)	24 (38.7)	33 (39.8)
Sex, *n* (%)			
Male	11 (52.4)	24 (38.7)	35 (42.2)
Ethnicity, *n* (%)			
Hispanic or Latino	1 (4.8)	10 (16.1)	11 (13.3)
Not Hispanic or Latino	20 (95.2)	52 (83.9)	72 (86.7)
Race, *n* (%)			
White	17 (81.0)	51 (82.3)	68 (81.9)
Nonwhite	4 (19.0)	11 (17.7)	15 (18.1)
Black or African American	3 (14.3)	5 (8.1)	8 (9.6)
Native Hawaiian or other Pacific Islander	0	0	0
Asian	0	1 (1.6)	1 (1.2)
American Indian or Alaska Native	0	0	0
Other	1 (4.8)	5 (8.1)	6 (7.2)
BMI, kg/m^2,[b] mean ± SD	20.85 ± 5.895	19.67 ± 3.643	19.97 ± 4.314

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Strawn J. Extended Release Guanfacine in Pediatric Anxiety Disorders: A Pilot, Randomized, Placebo-Controlled Trial. 2017.

Table 1. Demographic and Baseline Characteristics of Subjects

Characteristic	*Placebo (n=21)*	*GXR (n=62)*	*Total (n=83)*
BMI category,[c] *n* (%)			
Underweight	1 (4.8)	4 (6.5)	5 (6.0)
Normal	12 (57.1)	41 (66.1)	53 (63.9)
Overweight	4 (19.0)	14 (22.6)	18 (21.7)
Obese	4 (19.0)	3 (4.8)	7 (8.4)
Diagnosis, *n* (%)			
Generalized anxiety disorder	20 (95.2)	59 (95.2)	79 (95.2)
Separation anxiety disorder	14 (66.7)	29 (46.8)	43 (51.8)
Social anxiety disorder	16 (76.2)	41 (66.1)	57 (68.7)
Principal diagnosis,[d] *n* (%)			
Generalized anxiety disorder	7 (33.3)	28 (45.2)	35 (42.2)
Separation anxiety disorder	3 (14.3)	7 (11.3)	10 (12.0)
Social anxiety disorder	4 (19.0)	13 (21.0)	17 (20.5)
Combined	4 (19.0)	11 (17.7)	15 (18.1)
Other	3 (14.3)	3 (4.8)	6 (7.2)

[a]Age was calculated as the difference between the date of birth and the date of informed consent, truncated to years.

[b]BMI was calculated as [weight(kg)/height(m)^2].

[c]The BMI categories were derived by using the Centers for Disease Control BMI percentiles for children and adolescents; underweight = BMI <5th percentile; normal = 5th percentile up to <85th percentile; overweight = BMI 85th to <95th percentile; obese = BMI ≥95th percentile. For determining BMI categorization, age in months was calculated as the difference between the date of birth and the date of informed consent.

[d]The principal diagnosis was defined as the diagnosis with the highest clinical severity rating scale on the composite summary sheet. If ≥2 diagnoses had equal clinical severity ratings, the diagnosis that emerged first was named the principal diagnosis (i.e., generalized anxiety disorder, separation anxiety disorder, social anxiety disorder, or other).

BMI, body mass index; GXR, guanfacine extended-release; SD, standard deviation.

J.R. Strawn. Extended Release Guanfacine in Pediatric Anxiety Disorders: A Pilot, Randomized, Placebo-Controlled Trial. 2017.

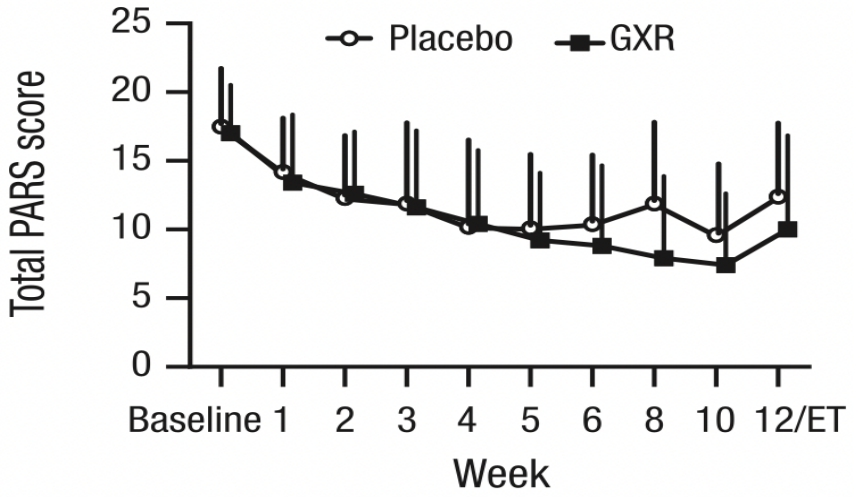
TABLE 2. TREATMENT-EMERGENT ADVERSE EVENTS (≥5%)

	Placebo (n = 21)		*GXR (n = 62)*	
Preferred term	n (%)	*No. of AEs*	n (%)	*No. of AEs*
Headache	4 (19)	7	22 (35.5)	26
Somnolence	1 (4.8)	2	17 (27.4)	30
Fatigue	0	0	13 (21.0)	16
Abdominal pain upper	2 (9.5)	2	10 (16.1)	17
Dizziness	1 (4.8)	2	7 (11.3)	8
Dizziness postural	0	0	7 (11.3)	11
Constipation	0	0	6 (9.7)	6
Decreased appetite	0	0	6 (9.7)	6
Sedation	2 (9.5)	2	6 (9.7)	7
Vomiting	1 (4.8)	1	6 (9.7)	7
Nausea	2 (9.5)	2	5 (8.1)	5
Diarrhea	2 (9.5)	2	4 (6.5)	6
Dry mouth	0	0	4 (6.5)	4
Initial insomnia	1 (4.8)	1	4 (6.5)	5
Irritability	1 (4.8)	1	4 (6.5)	4
Pharyngitis streptococcal	0	0	4 (6.5)	4
Cough	2 (9.5)	2	3 (4.8)	3
Upper respiratory tract infection	2 (9.5)	2	2 (3.2)	3
Increased appetite	2 (9.5)	2	1 (1.6)	1
Joint sprain	3 (14.3)	3	1 (1.6)	1

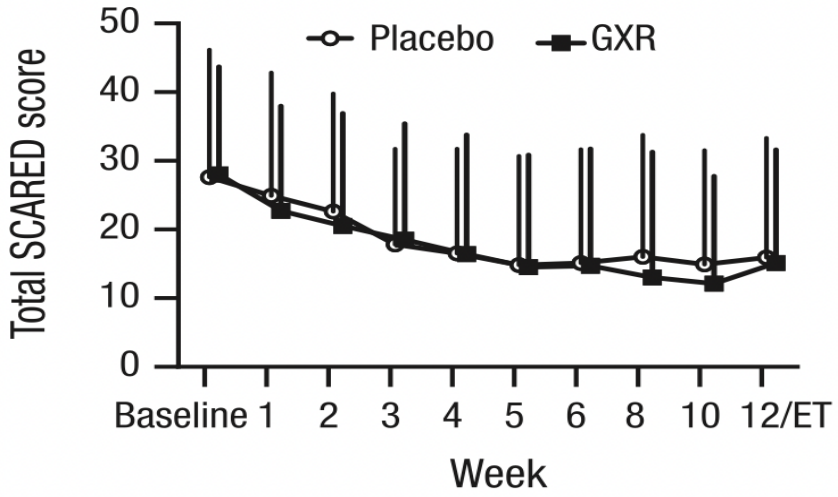
AEs, adverse events; GXR, guanfacine extended-release.

J.R. Strawn. Extended Release Guanfacine in Pediatric Anxiety Disorders: A Pilot, Randomized, Placebo-Controlled Trial. 2017.

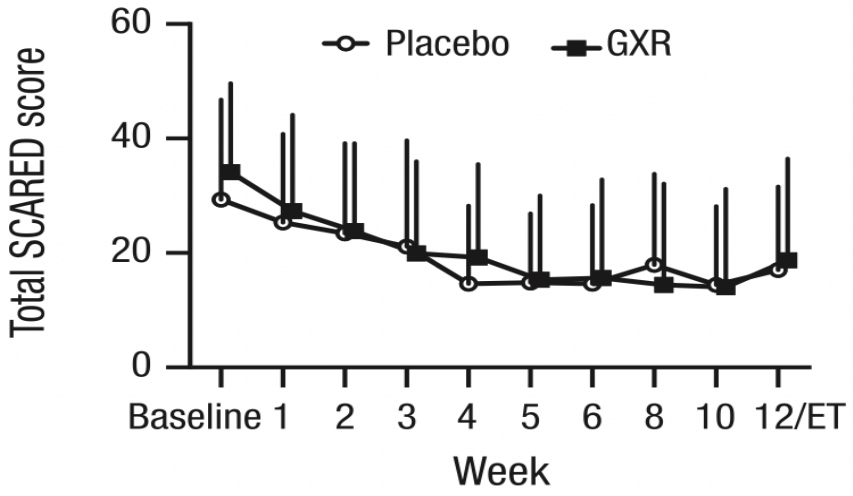
A **PARS**



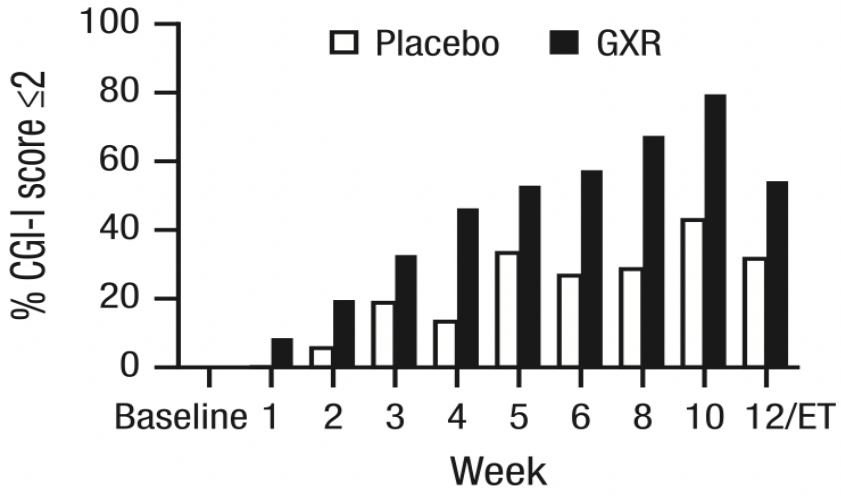
B **SCARED – Child**



C **SCARED – Parent**



D **CGI-I**



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)

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- **Method:** Systematic review of guidelines and clinical trial data on antidepressant (AD) treatment duration in pediatric patients with depressive and anxiety disorders.
- **Results:** For generalized, separation and social anxiety disorders, **6-9 months of AD treatment may be sufficient**, although many clinicians extend treatment to 12 months based on extrapolation for adults with anxiety disorders.
- **Conclusion:** Evidence based guidelines represent a starting point, but appropriate treatment varies and individual factors must be considered.

TABLE. Factors associated with a lower likelihood of response and/or remission in the long-term treatment of MDD and anxiety disorders in children and adolescents

Major depressive disorder	Anxiety disorders
More prior depressive episodes	Older age[15]
Residual symptoms after treatment (in adults)	Female sex[40]
Greater family levels of expressed emotion	Minority status[15]
Perceived family conflict	Baseline symptom severity[15,40]
Non-response to acute therapy (survey of outcomes following treatment for adolescent)	Lower socioeconomic status[40]
Depression study (unpublished)	
Female sex (survey of outcomes following treatment for adolescent depression study, unpublished)	Co-occurring internalizing disorder[15]
	Social anxiety disorder[15]
	Greater negative life events

Hathaway, E. et al. Curr Probl Pediatric Adolescent Health Care 2018;48:31-39

Key Points: Guidelines to Treatment of Pediatric Anxiety Disorders and OCD

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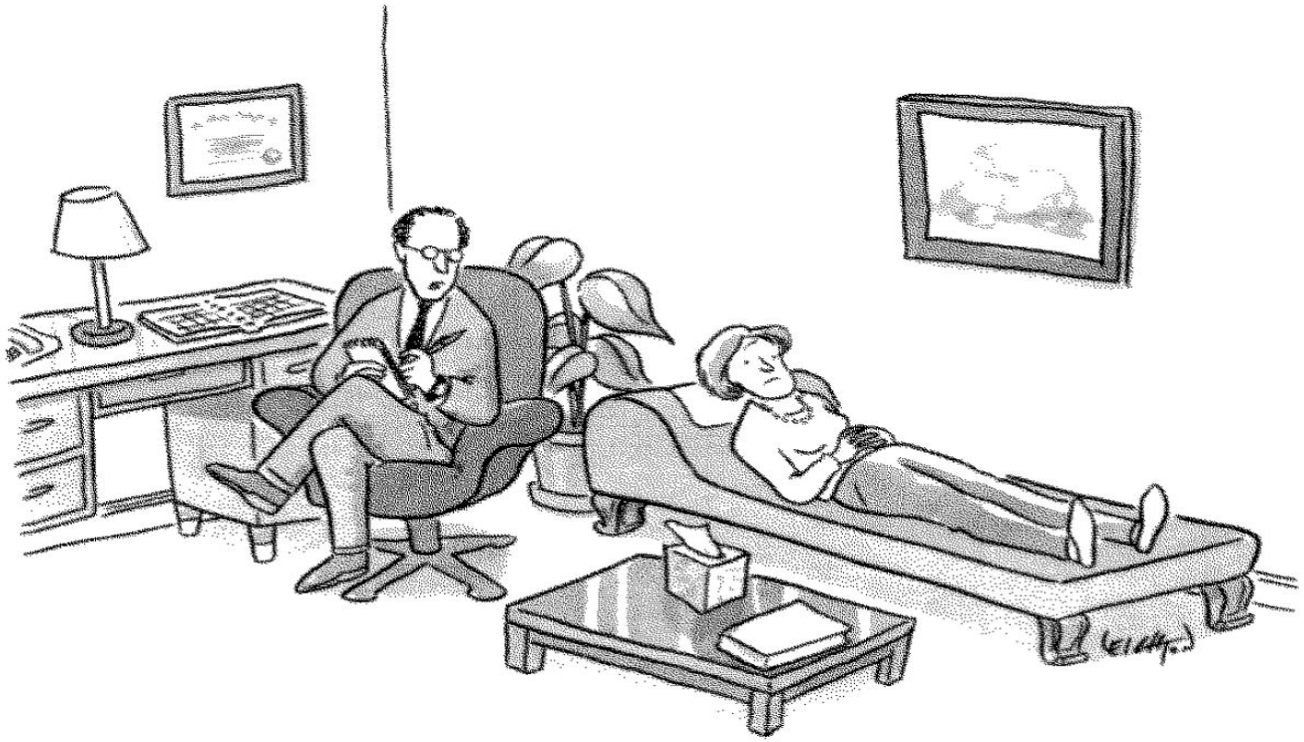
- **Begin with CBT** if symptoms are mild-moderate.
- For moderate to severe symptoms, begin with **SSRI of choice**, depending on family history of response, pharmacokinetics and adverse effects profile.
- **Start low** (i.e. 5-10 mg fluoxetine equivalents) and titrate gradually upward.
- **Therapeutic response**: Initial response can be seen in 2-4 weeks, but wait 8-12 weeks for full response.
- **Second line**: Reasonable to 1) switch to an **SNRI** (duloxetine, venlafaxine) and then2) extended release guanfacine.
- **Combination** of SSRI or SNRI and GXR may be helpful.
- **Augmentation** for partial response could be considered with buspirone, or possibly benzodiazepine or tricyclic antidepressants.

THE NEW YORKER



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

THURSDAY
SEPTEMBER 25

Treatment of Pediatric Anxiety Disorders: Summary

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- Anxiety disorders are **highly prevalent**, **early in onset**, and **highly comorbid** with **other anxiety disorders and mood disorders** in children and adolescents
- **Mild-moderate anxiety** symptoms are treated with CBT; for children and adolescents with at least moderate symptoms, psychopharmacological treatment is indicated.
- **Selective serotonin reuptake inhibitors (SSRIs)** are recommended as first line treatment for pediatric anxiety disorders; selective norepinephrine reuptake inhibitors (SNRIs) and alpha 2 agonists may also be considered.