

RX REFRESH

Pediatric Prescriber Pulse Check:
Test Your Psychopharmacology Know-How

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DEPRESSION

10,000 FOOT VIEW



50%

Adolescent clinical trials show 50% placebo response to non-specific clinical contact



33%

Antidepressant medication speeds improvement, but a third of patients do not reach full remission



25%

Greater chance to respond to SSRI than PBO, NNT with medications = 10



Which of the following has no evidence of improving depression in adolescents compared to placebo?

DATA ARE MIXED

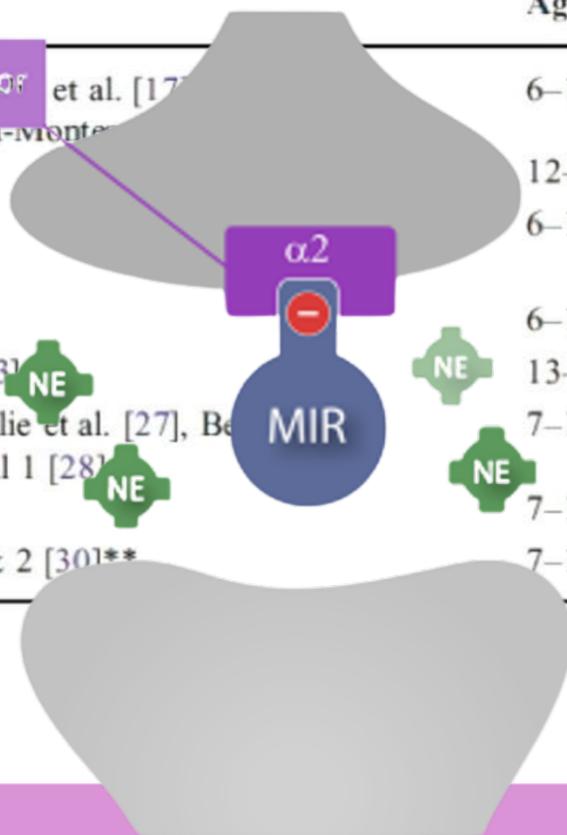
Mirtazapine blocks $\alpha 2$ presynaptic autoreceptors

Table 1 Controlled pediatric MDD studies

	Medication	Reference	Ages	Number of studies
Positive studies*	Fluoxetine	Emslie $\alpha 2$ autoreceptor et al. [17], TADS [19], Ammerlaan-Monte	6-17	1 (individual trials negative)
	Escitalopram	Emslie et al. [20]	12-17	
	Sertraline	Wagner et al. [22]**	6-17	
Negative studies	Escitalopram	Wagner et al. [21]	6-17	1
	Citalopram	von Knorring et al. [23]	13-18	1
	Paroxetine	Keller et al. [25], Emslie et al. [27], Be [26], Paroxetine Trial 1 [28]	7-17	4
	Venlafaxine	Emslie et al. [29]**	7-17	2
	Mirtazapine	Mirtazapine Trials 1 & 2 [30]**	7-17	2

*On primary outcome measure

**References 22, 29 and 30 include two trials in one paper



$\alpha 2$ presynaptic blockade

Loss of inhibition

increased NE release

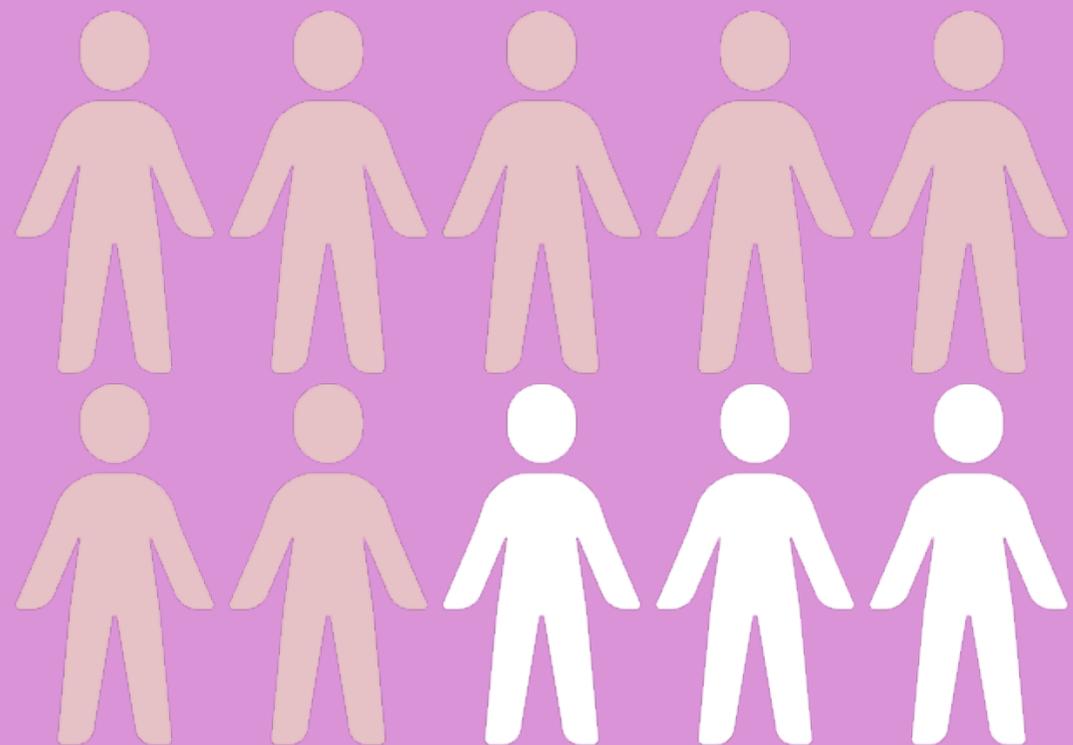
COMPARATIVE EFFICACY META-ANALYSIS



Cipriani A, et al. Comparative efficacy and tolerability of antidepressants for major depressive disorder in children adolescents: a network meta-analysis. *Lancet*. 2016 Aug 27;388(10047):881-90. doi: 10.1016/S0140-6736(16)30385-3. Epub 2016 Jun 8. PMID: 27289172.



According to a 2020 meta-analysis, which of the following antidepressants has the safest adverse effect profile in adolescents?



36%

Response rate for adolescents on 20 mg fluoxetine.



71%

Response rate for adolescents on 40–60 mg fluoxetine.



Heiligenstein JH, et al. Fluoxetine 40 -60 mg versus fluoxetine 20 mg in the treatment of children and adolescents with a less-than-complete response to nine-week treatment with fluoxetine 10 -20 mg: a pilot study. *J Child Adolesc Psychopharmacol*. 2006 Feb-Apr;16(1-2):207-17.

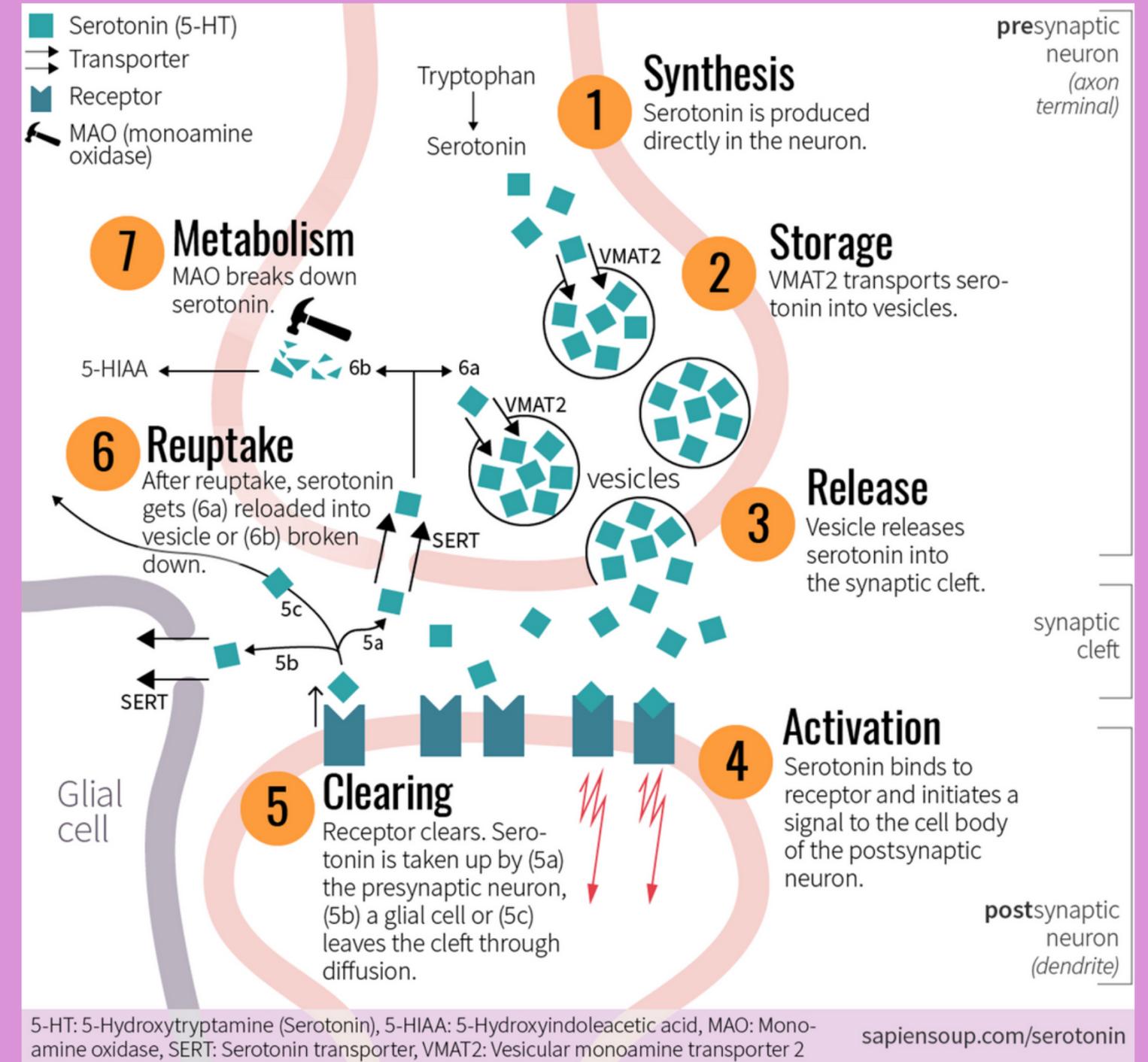
MECHANISM & AES

COMMON

GI Upset
 Headaches
 Easier Bruising
 Night Sweats
 Sedation or activation
 Sexual Dysfunction

SERIOUS

Serotonin Syndrome
 Black Box Warning



ANXIETY



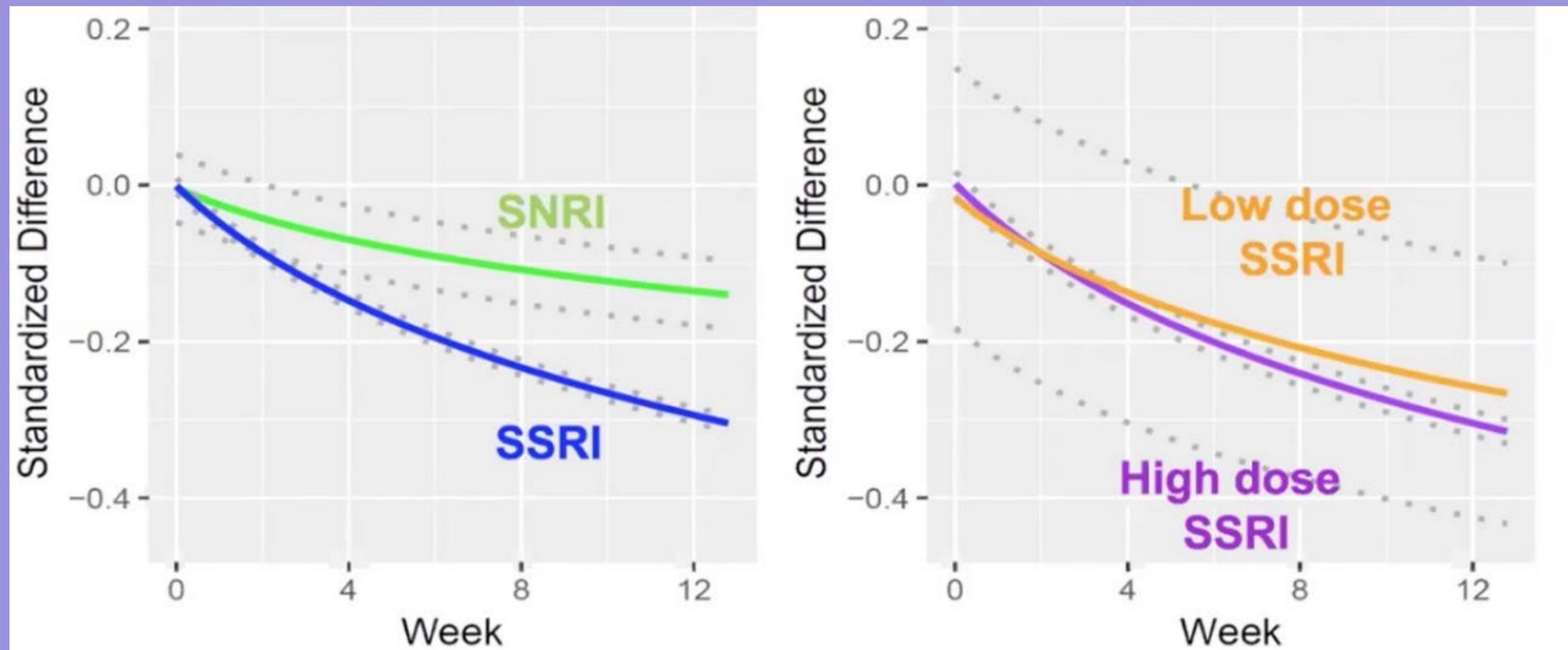
Source	Hedges g	SE (95% CI)
Depressive disorders		
SSRI		
Atkinson et al, ⁴⁸ 2014	0.05	0.17 (-0.27 to 0.38)
Emslie et al, ⁴⁹ 2014	0.07	0.19 (-0.29 to 0.44)
PIR112487, ⁴⁷ 2011	0.34	0.27 (-0.18 to 0.87)
Emslie et al, ⁴⁵ 2009	0.21	0.11 (-0.01 to 0.43)
Findling et al, ⁴⁶ 2009	0.35	0.39 (-0.42 to 1.11)
von Knorring et al, ⁴³ 2006	0.00	0.13 (-0.25 to 0.26)
Wagner et al, ²³ 2006	0.14	0.12 (-0.10 to 0.38)
Berard et al, ⁴¹ 2006	0.08	0.13 (-0.18 to 0.33)
Emslie et al, ⁴² 2006	0.05	0.14 (-0.22 to 0.33)
Wagner et al, ²² 2004	0.37	0.15 (0.07 to 0.67)
March et al, ⁴⁰ 2004	0.40	0.17 (0.07 to 0.72)
Wagner et al, ³⁹ 2003	0.19	0.11 (-0.02 to 0.39)
Emslie et al, ³⁸ 2002	0.52	0.14 (0.25 to 0.80)
Keller et al, ³⁷ 2001	0.21	0.15 (-0.08 to 0.51)
Emslie et al, ³⁶ 1997	0.60	0.21 (0.19 to 1.00)
Simeon et al, ³⁵ 1990	0.21	0.36 (-0.49 to 0.91)
Subtotal	0.21	0.04 (0.13 to 0.29)

Anxiety disorders		
SSRI		
Melvin et al, ⁵⁹ 2017	0.47	0.31 (-0.14 to 1.07)
da Costa et al, ⁵⁷ 2013	1.11	0.45 (0.23 to 2.00)
Walkup et al, ⁵⁶ 2008	0.32	0.18 (-0.04 to 0.68)
Wagner et al, ⁵³ 2004	0.72	0.18 (0.49 to 0.95)
Birmaher et al, ⁵² 2003	0.53	0.23 (0.08 to 0.99)
RUPP, ⁵⁰ 2001	1.06	0.19 (0.69 to 1.43)
Rynn et al, ⁵¹ 2001	1.48	0.47 (0.56 to 2.39)
Subtotal	0.71	0.13 (0.45 to 0.97)



Current evidence in pediatric anxiety management suggests:

PRECISION



SSRI vs SNRI

Faster and larger improvement with SSRI

FDA Approval
Duloxetine (SNRI)

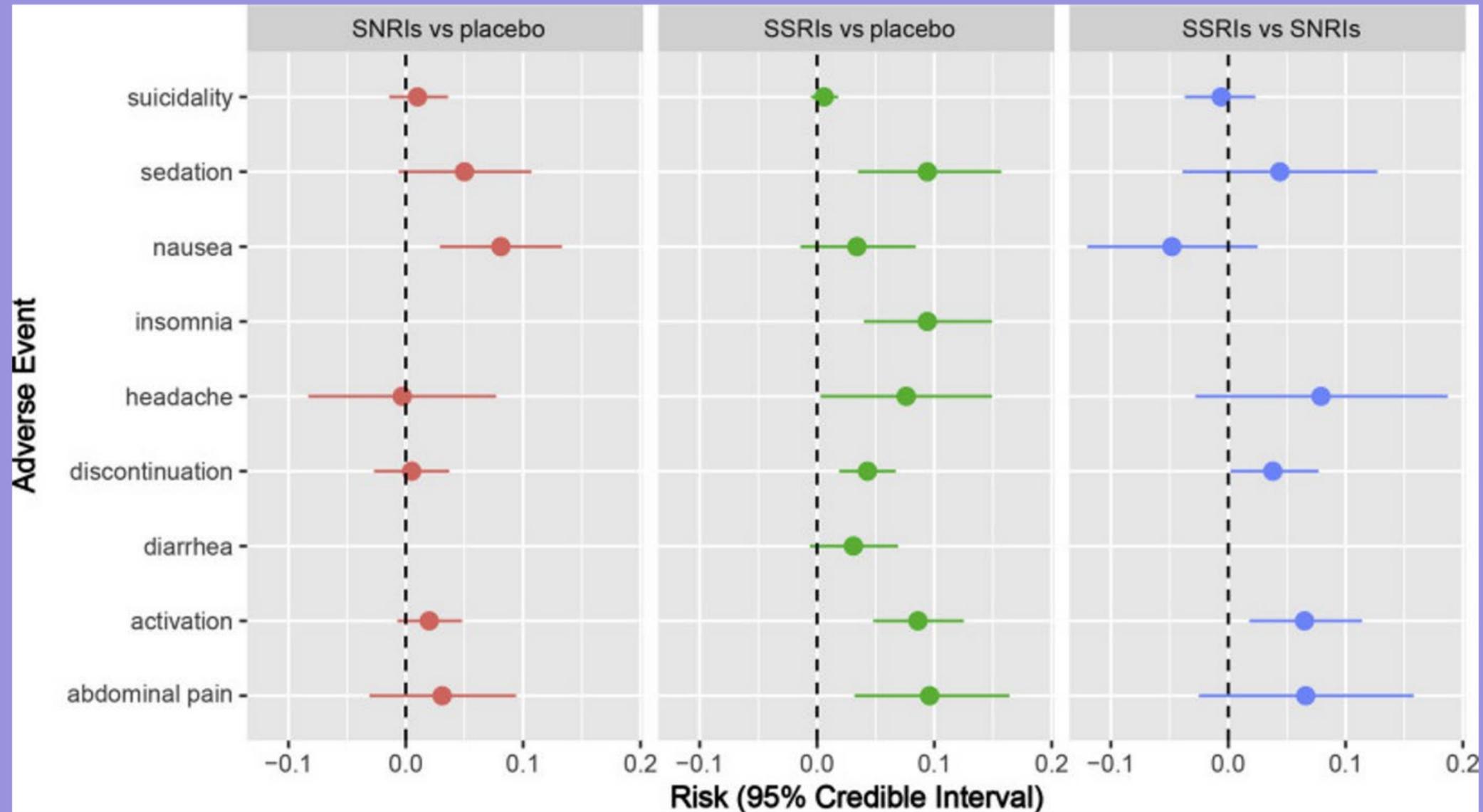
Dosage less
important

Pharmacokinetics and
dynamics may explain
individual variation



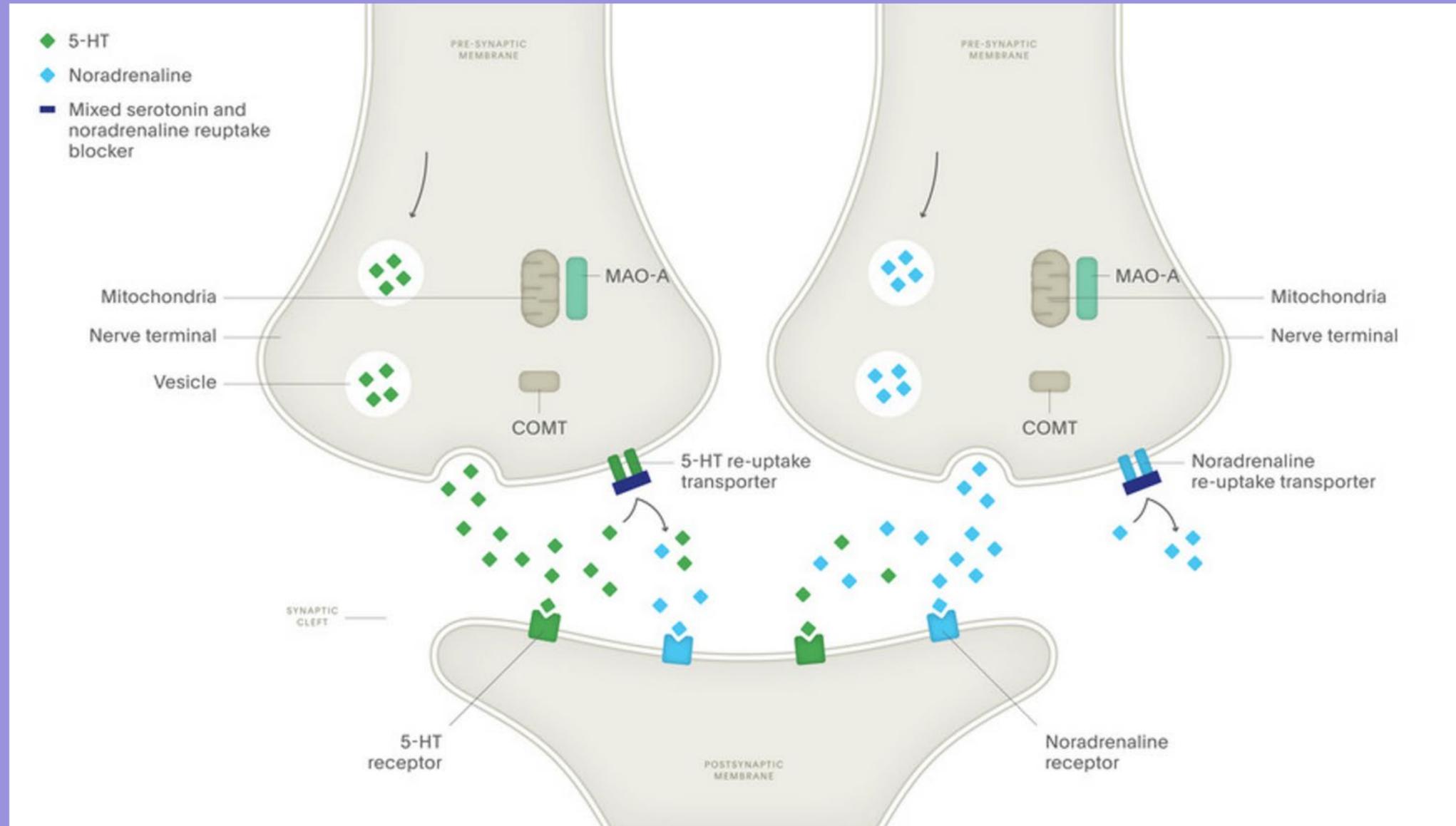
**An adolescent on fluoxetine for anxiety presents with activation.
Which medication is the next best choice to avoid this adverse
effect?**

TOLERABILITY



Mills JA, Strawn JR. Antidepressant tolerability in pediatric anxiety and obsessive - compulsive disorders: A Bayesian hierarchical modeling meta - analysis. J Am Acad Child Adolesc Psychiatry. 2020;59:1240 - 1251.

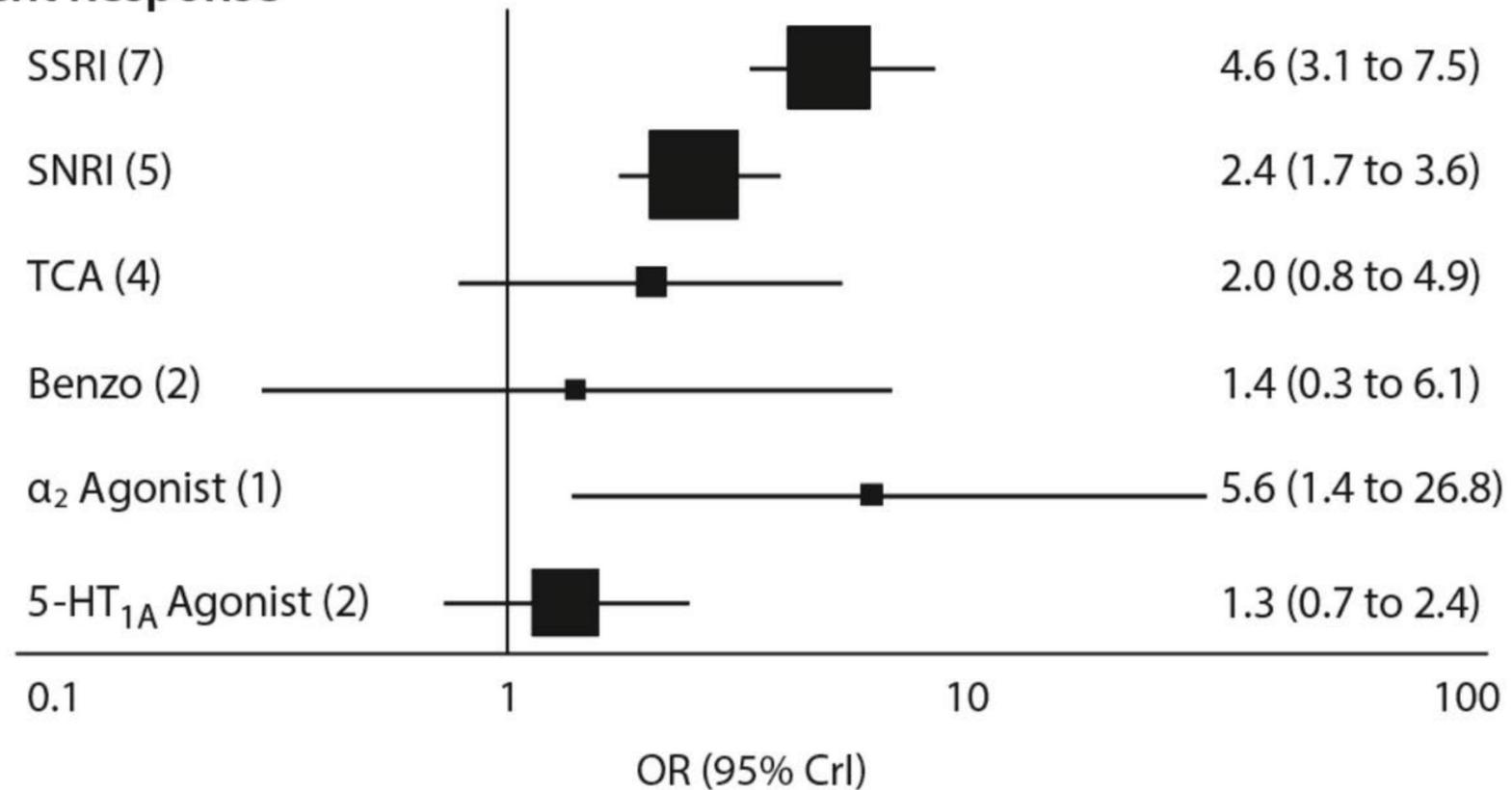
SNRI: MECHANISM OF ACTION



EFFICACY: PEDIATRIC ANXIETY

Figure 2. Forest Plot of Medication Class Efficacy Relative to Placebo for Treatment Response (A) and Anxiety Symptom Improvement (B)^a 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





A 10-year-old child presents with symptoms meeting criteria for both ADHD and generalized anxiety disorder. Which of the following statements is most consistent with current evidence regarding treatment sequencing?

ANXIETY AND ADHD

	SSRI and Stimulant		Placebo and Stimulant		Random Regression Results: Comparison of Responder Rates at End of Double-Blind Phase
	End of Stabilization	End of Double-Blind	End of Stabilization	End of Double-Blind	
SNAP-IV Parent and Teacher ADHD, mean (SD) [no.]	0.96 (0.65) [15]	0.87 (0.53) [14]	1.09 (0.70) [10]	1.24 (0.74) [10]	$F(1, 22)$ treatment x time = 0.67; $p = .42$ $F(1, 22)$ time = .07; $p = .79$
PARS Total score, mean (SD) [no.]	15.73 (3.41) [15]	10.20 (7.37) [15]	15.00 (2.31) [10]	12.10 (4.25) [10]	$F(1, 146)$ treatment x time = 1.46; $p = .23$ $F(1, 146)$ time = 9.25; $p = .006$
Clinical Global Impressions - Anxiety-Improvement, no. (%)					
Responder	1 (7)	10 (67)	2 (20)	5 (50)	$\chi^2_1 = .03$; $p = .87$
Non-responder	14 (93)	5 (33)	8 (80)	5 (50)	
Joint PARS and Clinical Global Impressions-I Anxiety criteria, no. (%)					
Responder	0 (0)	7 (47)	0 (0)	5 (50)	$\chi^2_1 = .69$; $p = .40$
Non-responder	15 (100)	8 (53)	10 (100)	5 (50)	



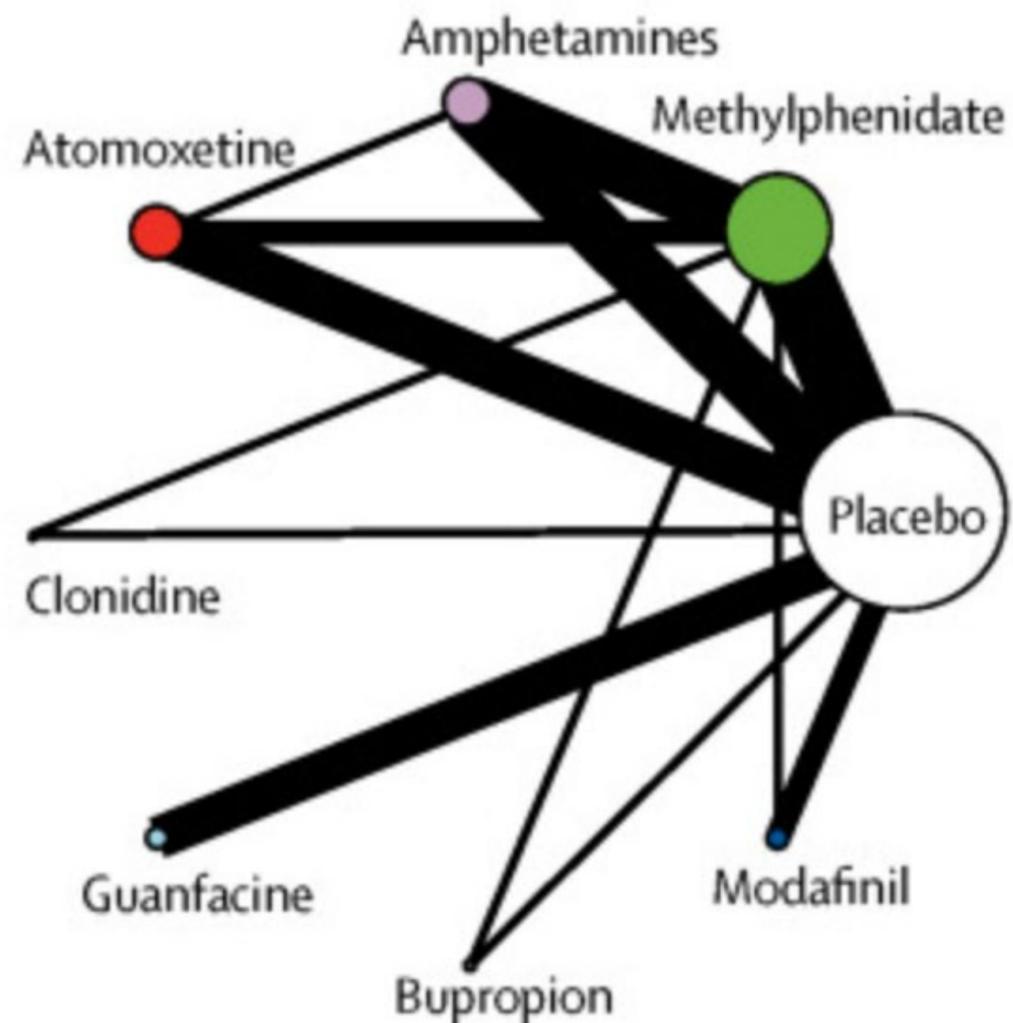
ADHD





According to a 2018 meta-analysis, which drug was more acceptable, more effective, and had fewer side effects than placebo in adolescents with ADHD?

Tolerability



UCortese S, Adamo N, DeI Giovane C, et al. Comparative efficacy and tolerability of medications for attention-deficit hyperactivity disorder in children, adolescents, and adults: A systematic review and network meta-analysis. *Lancet Psychiatry*. 2018;5:727-738.



COMMON SIDE EFFECTS

- Transient headache
- Insomnia
- Transient stomachache
- Decreased appetite
- Behavioral rebound
- Increase in heart rate and blood pressure

LESS COMMON SIDE EFFECTS

- Vomiting
- Emotional lability
- Psychosis, hallucinations, and mania



In s o m n i a

- Earlier Dosing
- XR to IR
- Alpha Agonist

A p p e t i t e S u p p r e s s i o n

- Cyproheptadine QHS
- Stimulant AFTER meals
- Play with formulation

D e l a y e d G r o w t h

- Drug Holidays
- Prioritize nutrition

I r r i t a b i l i t y

- Switch formulation
- Add IR for coming off



ADHD and Substance Use Risk

- ADHD significantly increases risk of SUD
- Stimulant treatment does not worsen risk of SUD, but is not protective
- Some evidence suggests early initiation of stimulants might confer some benefit
- Inconsistent use and diversion predict increased risk of SUD

Humphreys K.L., Eng T., Lee S.S. Stimulant medication and substance use outcomes: a meta-analysis. *JAMA Psychiatry*. 2013;70(7):740–749.

McCabe SE, Dickinson K, West BT, Wilens TE. Age of Onset, Duration, and Type of Medication Therapy for Attention-Deficit/Hyperactivity Disorder and Substance Use During Adolescence: A Multi-Cohort National Study. *J Am Acad Child Adolesc Psychiatry*. 2016 Jun;55(6):479-86.

Atomoxetine: Clinical Overview

- **Mechanism of Action:** Norepinephrine reuptake inhibitor
- **FDA-approved Indications:** ADHD
- **Typical Dosage Range:** 10-100 mg/day
- **Onset of Action:** 2-4 weeks
- **Common Side Effects:** Insomnia, decreased appetite
- **Pharmacokinetics:** Half-life ~5 hours
- **Special Considerations:** Less responsiveness if stimulant non responder
- **Comorbidities**
 - Anxiety
 - Tics

Viloxazine: Clinical Overview

- **Mechanism of Action:** Norepinephrine and serotonin reuptake inhibitor
- **FDA-approved Indications:** ADHD, major depressive disorder
- **Typical Dosage Range:** 100-400 mg/day
- **Onset of Action:** 1-2 weeks
- **Common Side Effects:** Fatigue, somnolence
- **Pharmacokinetics:** Half-life ~10 hours
- **Drug Interactions:** Strong CYP1A2 inhibitor (duloxetine contraindicated)
- **Special Considerations:** Contraindicated in severe liver impairment



BUPROPION

- NDRI
- Comorbid depression/cognitive slowing

PATCHES

- Dextro - amphetamine transdermal patch (~9 hours)
 - multiple sites for application

ER DEXTROAMPHETAMINE/AMPHETAMINE



- Very extended coverage
- 16 hours (onset 2 -4 hours)
- 12.5-25 mg/day
 - Capsules: 12.5, 25, 37.5, 50 mg
- Triple bead delivery system

AACAP PARENT MEDICATION GUIDE



Stimulant Medications

Stimulants are the most effective and most commonly prescribed medications for ADHD. They include both amphetamine (Adderall, Vyvanse, Dexedrine, and others) and methylphenidate (Ritalin, Concerta, Focalin, and others). (See Table 1 for full list.) Research shows that

more available to boost the “signal.” Stimulants affect the availability of certain neurotransmitters—dopamine and norepinephrine—that play an important role in attention.

Forms and dosing. The good news is that there are many forms (preparations) of stimulants available; however, this can

Table 1. Stimulant Medications

Methylphenidate (MPH) for ADHD					
Medication	Starting Dose	How Supplied	Dosage Form	Duration of Medication Effects	Given how many times a day?
Adhansia XR	25 mg	25, 35, 45, 55, 70, 85 mg	capsules	Up to 16 hours	Once
Aptensio XR	10 mg	10, 15, 20, 30, 40, 50, 60 mg	capsules	12 hours	Once
Azstarys XR	26.1/5.2 mg	26.1/5.2, 39.2/7.8, 52.3/10.4 mg	capsules	12 hours	Once
Concerta	18 mg	18, 27, 36, 54 mg	capsules	12 hours	Once
Contempla XR	8.6 mg	8.6, 17.3, 25.9 mg	disintegrating tablets	12 hours	Once
Daytrana	10 mg	10, 15, 20, 30 mg	patch	6–16 hours	Once
Focalin	2.5 mg	2.5, 5, 10 mg	tablets	4–5 hours	Two to three times
Focalin XR	5 mg	5, 10, 15, 20 mg	capsules	10–12 hours	Once
Jornay PM	20 mg	20, 40, 60, 80, 100 mg	delayed-release capsules	12 hours	Once
Metadate CD	20 mg	10, 20, 30, 40, 50, 60 mg	capsules	8 hours	Once
Quillivant	<10 mg	25 mg	suspension	12 hours	Once
Quilichew	<10 mg	20, 30, 40 mg	chewable tablets	8 hours	Once
Ritalin IR	5 mg	5, 10, 20 mg	tablets	3–4 hours	Two to four times
Ritalin LA	20 mg	10, 20, 30, 40 mg	capsules	8 hours	Once
Amphetamine (AMPH) for ADHD					
Medication	Starting Dose	How Supplied	Dosage Form	Duration of Medication Effects	Given how many times a day?
Adderall	2.5–5 mg	5–30 mg	tablets	6 hours	Once to twice

SLEEP



SLEEP PROBLEMS ARE PERVASIVE

- $\frac{1}{3}$ of children and adolescents report sleep problems interfering with activities of daily living
 - ~25% of these individuals receive pharmacological intervention
- Insomnia has significant overlap with youth with mental health conditions
 - Chicken or egg?
 - When we treat insomnia in kids, we see decreased psychopathology down the road



A 9-year-old child is seen for chronic difficulty falling asleep despite good sleep hygiene. Which of the following statements is most consistent with current evidence regarding melatonin use in children with sleep-onset insomnia?

THERE ARE NO FDA APPROVED MEDICATIONS FOR PEDIATRIC INSOMNIA

Medications provide 15-45 minutes
of additional sleep

Decrease sleep latency
~15 minutes

Anterograde amnesia contributes
to feeling more rested

MEDICATIONS

Prescription

- BZD
- Non-BZD receptor agonists*
- Melatonin receptor agonists*
- Alpha agonists*
- Antidepressants
- Doxepin
- Antipsychotics*
- Anticonvulsants
- Orexin antagonists

OTC

- Antihistamines*
- Melatonin*
- Herbal medications/supplements



MELATONIN

- From tryptophan
- Hypnotic (MT1) and chronobiotic (MT2) properties
- Blocked by blue light
- Plasma levels peak 1 hour post dosage
- Half life ~45 minutes
- Minimal effects on sleep architecture



Melatonin for Pediatric Sleep-Onset Insomnia (2010)

Dose-Finding RCT (ages 6–12)

- **Design** : RCT, N=72
- **Intervention**: melatonin 0.05–0.15 mg/kg vs placebo
- **Effect** : Sleep onset ~1 hour earlier; latency ↓ 40–50 min
- **Dose** : No added benefit above 0.05 mg/kg
- **Key insight** : Timing > dose (chronobiotic effect)
- **Clinical takeaway**: Start low (1–2 mg), give 1–2 h before bedtime
- USP verified

van Geijlswijk IM, van der Heijden KB, Egberts AC, Korzilius HP, Smits MG. Dose finding of melatonin for chronic idiopathic childhood sleep onset insomnia: an RCT. *Psychopharmacology (Berl)*. 2010 Oct;212(3):379-91.



MELATONIN

Hypnotic (early/middle insomnia)

- 100 mcg - 1 mg (young)
- 2.5-3 mg (middle)
- 5-10 mg adolescents/young adults/neurodiverse

Chronobiotic (delayed sleep phase disorder)

- .1-.5 mg 4-5 hours before desired bed time (DLMO)

Jet Lag

- From tryptophan
- Hypnotic (MT1) and chronobiotic (MT2) properties



ADVERSE EFFECTS

Morning Sedation

Enuresis

****Beware CYP1A2 Interactions**

Dizziness

Headache

GI





ALPHA AGONISTS

- Decreased noradrenergic tone
- Peak effect 2-4 hours
- AEs: hypotension, dry mouth
- Tolerance is common
- Rebound

ANTI HISTAMINES

- Histamine receptor antagonists
- Anticholinergic AEs
- Tolerance is common
- Paradoxical excitation (younger)
- 2 pediatric studies: minimal effect

THANK
YOU!