Pediatric Collaborative Care Behavioral Health Conference 2023-2024

Text: 608-260-7097

Code: FEYGOZ

Please text to record your attendance and claim credit. Even if you do not need the credit, please text in to record your attendance!

Need support? Email Kate Dougherty at catherine.dougherty@wisc.edu or Stacey Parker at skparker2@wisc.edu

Department of Pediatrics
UNIVERSITY OF WISCONSIN
SCHOOL OF MEDICINE AND PUBLIC HEALTH

Text: 608-260-7097

Code: FEYGOZ

School of Medicine and Public Health
UNIVERSITY OF WISCONSIN–MADISON

“Next Steps For Adolescent Anxiety and Depression When SSRIs Are Not a Good Fit: SNRIs, Bupropion and Mirtazapine”

William B. Taft MD
Clinical Associate Professor of Psychiatry and Pediatrics
Director, Child and Adolescent Psychiatry Consult/Liaison Service
UW-Madison School of Medicine and Public Health

Conflict of Interest

The planner and speaker of this CE activity has no relevant financial relationships with ineligible companies to disclose.

The speaker does intend to discuss any unlabeled or unapproved use of drugs or devices.

Please take a moment at the end of the session to complete your evaluation.

Thank you!

Department of Pediatrics
UNIVERSITY OF WISCONSIN
SCHOOL OF MEDICINE AND PUBLIC HEALTH

Text: 608-260-7097
Code: FEYGOZ

School of Medicine and Public Health
UNIVERSITY OF WISCONSIN–MADISON

Objectives

- Summarize the pediatric indications and evidence-based off-label uses for SNRIs, bupropion and mirtazapine
- Discuss pros and cons of adding bupropion or mirtazapine to a partially helpful SRI
- Describe dosing schedules and strategies for switching antidepressants

Spoiler Alert!

- None of the medications discussed today have FDA-approved indications in children or adolescents

SNRIs

Venlafaxine
Desvenlafaxine
Duloxetine
Levomilnacipran

- Similar clinical effects as SSRIs
- Calming, decreasing repetitive thoughts
- Depression data generally better than the anxiety data in youth
- Probably less “activating” than SSRIs
- Probably less weight gain risk than SSRIs
- 2-4 weeks for response for anxiety, 4 weeks for depression

SNRIs

Venlafaxine
Desvenlafaxine
Duloxetine
Levomilnacipran

- Digestive side effects
- Sleep changes
- Hypertension
- Withdrawal/zaps
- Emotional blunting
- Disinhibition
- Aggression
- Black Box for suicidality

Venlafaxine

- IR, XR formulations, no liquid
- Dose range 37.5mg-225mg daily
- FDA Approved for MDD, GAD, Social Anxiety, Panic Disorder

- Short half-life

- Some evidence in ADHD, OCD, pain disorders in youth, very small studies of agitation in Autism.

Desvenlafaxine

- Once daily extended-release tablet
- Dose range 50-100mg, no titration recommended
- FDA Approved for MDD

- Active metabolite of venlafaxine
- Few cytochrome P450 interactions

- Very little data other than for depression

Duloxetine

- Once daily extended-release capsule
- Dose range 30-120mg
- FDA approved for MDD, GAD, fibromyalgia, diabetic neuropathy, chronic musculoskeletal pain

- 2D6 and 1A2 interactions

- Adolescent evidence is strongest for anxiety
- Some evidence of help for headaches, spinal cord injury pain, bingeing, pilot data in ADHD

Levomilnacipran

- Once daily extended-release capsules
- Dose range 20-120mg
- FDA Approved for MDD

- 3A4 substrate

- I was unable to find any published pediatric studies, there is at least one negative unpublished study

Mirtazapine

- Centrally-acting α_2 antagonist
- serotonin 2 antagonism
- H1 antagonism
- Moderate α_1 antagonism
- Moderate antimuscarinic

- Sleepiness
- Hungriness
- Constipation
- Hyperlipidemia

Mirtazapine

- Once daily, usually at bedtime
- Dose range 7.5-45mg
- FDA approved for MDD

- Limited pediatric data, mostly for sleep

Bupropion

- Norepinephrine/Dopamine reuptake inhibitor

- Headache
- Insomnia
- Weight loss
- Hypertension
- Irritability
- Seizures (0.4% at 450mg/d)

Bupropion

- IR, twice-daily SR and once daily XR forms
- Dose range 150-450mg
- FDA approved in MDD

- Available formulations limit use in children
- Unreliable for anxiety, but sometimes it helps
- Contraindicated in seizure disorders, bulimia or anorexia, or during withdrawal symptoms

- ADHD, smoking cessation, combination weight loss medications

Switch or Augment?

School of Medicine
and Public Health
UNIVERSITY OF WISCONSIN–MADISON

Reasons to Switch

- No response to initial agent after “a reasonable trial”
- Side effects
- Treatment emergent suicidality
- Non-adherence
- Coverage/cost
- Unreliable supply

Reasons to Augment

- Partial improvement in the primary symptoms
- Improvement in one diagnosis, but not another
- Patient preference
- Targeting residual symptoms
- Fewer side effects with lower doses of two medications than higher dose of just one

Combination Treatment

- Pediatric data limited
- Adult studies of combination treatment for depression are not encouraging, mostly showing that augmenting is no better or worse than using a single agent
- Very limited data on anxiety

Making the Switch

School of Medicine
and Public Health
UNIVERSITY OF WISCONSIN–MADISON

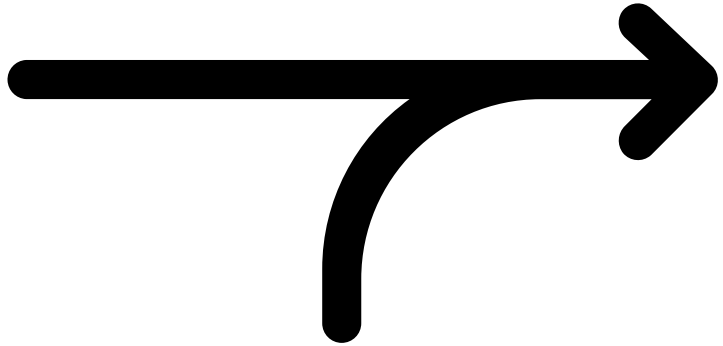
Medication-specific Considerations

- Half-life
- Withdrawal symptoms
- Overlapping receptor effects
- Overlapping side effects
- Time to response
- Time to side effects

Addition

Pros

- Make one change at a time
- Preserve effect of prior agent



Cons

- Polypharmacy
- Inertia—is the first medicine actually helping?

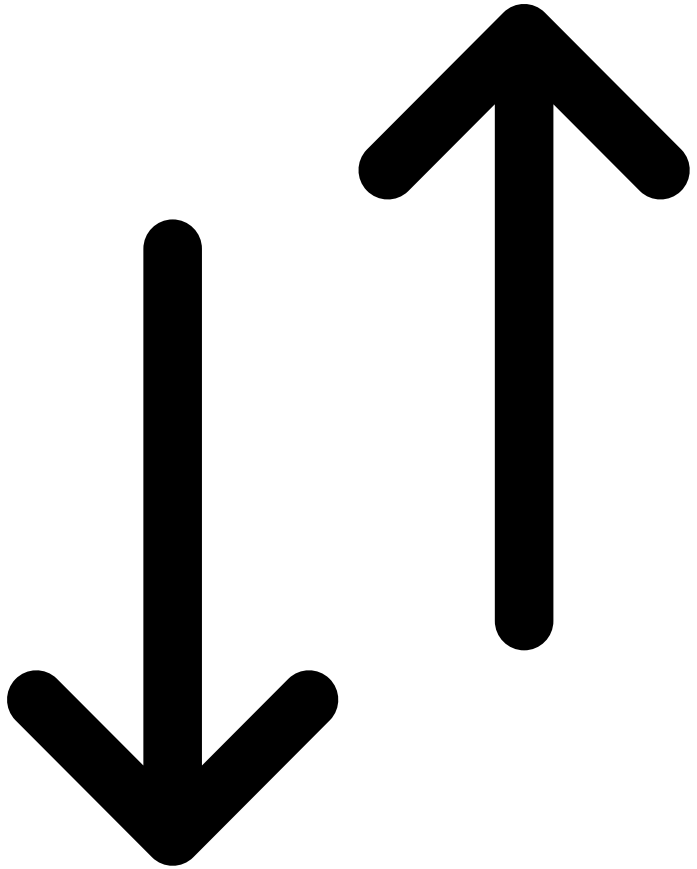
Substitution

Pros

- Best when turning to another medication in the same class
- Fastest

Cons

- Risk of withdrawal
- Making two changes at once



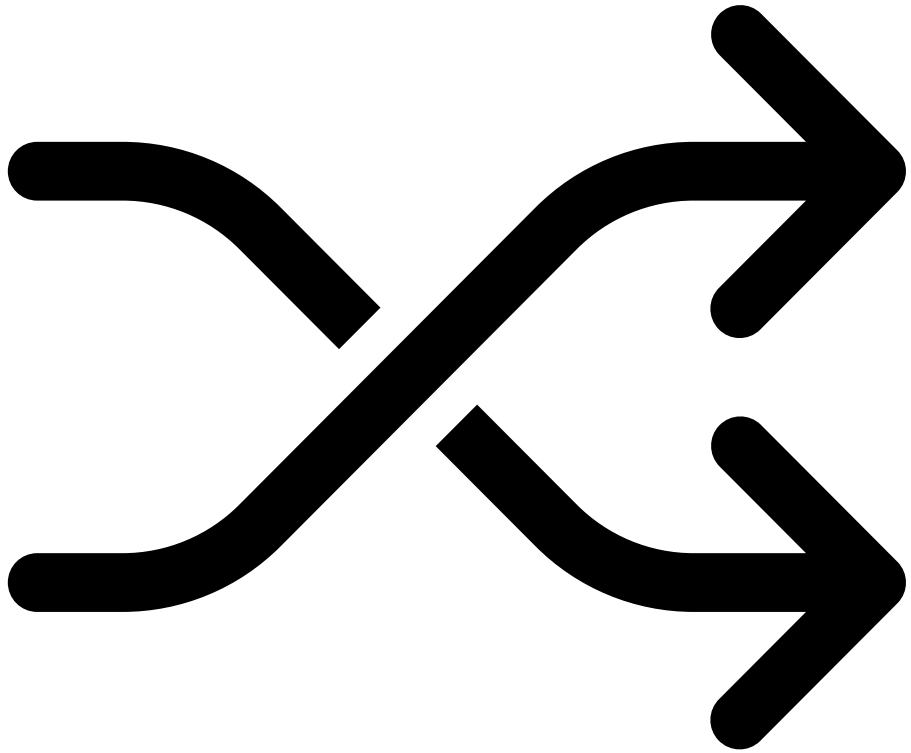
Cross-Taper

Pros

- Minimize risk of withdrawal
- Minimize risk of overlap side effects

Cons

- Risk of a nadir between the two agents
- Making two changes at once
- feeling better at the midpoint



References

- Accessdata.fda.gov
- Atkinson S, Lubaczewski S, Ramaker S, England RD, Wajsbrot DB, Abbas R, Findling RL. Desvenlafaxine Versus Placebo in the Treatment of Children and Adolescents with Major Depressive Disorder. J Child Adolesc Psychopharmacol. 2018 Feb;28(1):55-65. doi: 10.1089/cap.2017.0099. Epub 2017 Nov 29. PMID: 29185786; PMCID: PMC5771531.
- Emslie GJ, Findling RL, Yeung PP, Kunz NR, Li Y. Venlafaxine ER for the treatment of pediatric subjects with depression: results of two placebo-controlled trials. J Am Acad Child Adolesc Psychiatry. 2007 Apr;46(4):479-488. doi: 10.1097/chi.0b013e31802f5f03. PMID: 17420682.
- Emslie GJ, Mayes T, Porta G, Vitiello B, Clarke G, Wagner KD, Asarnow JR, Spirito A, Birmaher B, Ryan N, Kennard B, DeBar L, McCracken J, Strober M, Onorato M, Zelazny J, Keller M, Iyengar S, Brent D. Treatment of Resistant Depression in Adolescents (TORDIA): week 24 outcomes. Am J Psychiatry. 2010 Jul;167(7):782-91. doi: 10.1176/appi.ajp.2010.09040552. Epub 2010 May 17. PMID: 20478877; PMCID: PMC3257891.
- Emslie GJ, Prakash A, Zhang Q, Pangallo BA, Bangs ME, March JS. A double-blind efficacy and safety study of duloxetine fixed doses in children and adolescents with major depressive disorder. J Child Adolesc Psychopharmacol. 2014 May;24(4):170-9. doi: 10.1089/cap.2013.0096. Epub 2014 May 9. PMID: 24815533; PMCID: PMC4026396.
- Hetrick SE, McKenzie JE, Bailey AP, Sharma V, Moller CI, Badcock PB, Cox GR, Merry SN, Meader N. New generation antidepressants for depression in children and adolescents: a network meta-analysis. Cochrane Database Syst Rev. 2021 May 24;5(5):CD013674. doi: 10.1002/14651858.CD013674.pub2. PMID: 34029378; PMCID: PMC8143444.
- Kessler DS, MacNeill SJ, Tallon D, Lewis G, Peters TJ, Hollingworth W, Round J, Burns A, Chew-Graham CA, Anderson IM, Shepherd T, Campbell J, Dickens CM, Carter M, Jenkinson C, Macleod U, Gibson H, Davies S, Wiles NJ. Mirtazapine added to SSRIs or SNRIs for treatment resistant depression in primary care: phase III randomised placebo controlled trial (MIR). BMJ. 2018 Oct 31;363:k4218. doi: 10.1136/bmj.k4218. Erratum in: BMJ. 2018 Nov 15;363:k4691. PMID: 30381374; PMCID: PMC6207929.
- Martin *Pediatric Psychopharmacology, 2nd edition*
- March JS, Entusah AR, Rynn M, Albano AM, Tourian KA. A Randomized controlled trial of venlafaxine ER versus placebo in pediatric social anxiety disorder. Biol Psychiatry. 2007 Nov 15;62(10):1149-54. doi: 10.1016/j.biopsych.2007.02.025. Epub 2007 Jun 5. PMID: 17553467.
- Ng QX. A Systematic Review of the Use of Bupropion for Attention-Deficit/Hyperactivity Disorder in Children and Adolescents. J Child Adolesc Psychopharmacol. 2017 Mar;27(2):112-116. doi: 10.1089/cap.2016.0124. Epub 2016 Nov 4. PMID: 27813651.
- Rao Y, Yang R, Zhao J, Cao Q. Efficacy and tolerability of antidepressant drugs in treatment of depression in children and adolescents: a network meta-analysis. Zhejiang Da Xue Xue Bao Yi Xue Ban. 2022 Aug 1;51(4):480-490. English. doi: 10.3724/zdxbyxb-2022-0145. PMID: 37202104; PMCID: PMC10264982. (abstract available in English, full paper in Chinese)
- Rush AJ, Trivedi MH, Stewart JW, Nierenberg AA, Fava M, Kurian BT, Warden D, Morris DW, Luther JF, Husain MM, Cook IA, Shelton RC, Lesser IM, Kornstein SG, Wisniewski SR. Combining medications to enhance depression outcomes (CO-MED): acute and long-term outcomes of a single-blind randomized study. Am J Psychiatry. 2011 Jul;168(7):689-701. doi: 10.1176/appi.ajp.2011.10111645. Epub 2011 May 2. PMID: 21536692.
- Rynn MA, Riddle MA, Yeung PP, Kunz NR. Efficacy and safety of extended-release venlafaxine in the treatment of generalized anxiety disorder in children and adolescents: two placebo-controlled trials. Am J Psychiatry. 2007 Feb;164(2):290-300. doi: 10.1176/ajp.2007.164.2.290. PMID: 17267793.
- Saito T, Ishida M, Nishiyori A, Ochiai T, Katagiri H, Matsumoto H. Efficacy and Safety of Duloxetine in Children and Adolescents with Major Depressive Disorder in Japan: A Randomized Double-Blind Placebo-Controlled Clinical Trial Followed by an Open-Label Long-Term Extension Trial. J Child Adolesc Psychopharmacol. 2022 Apr;32(3):132-142. doi: 10.1089/cap.2021.0104. Epub 2022 Mar 18. PMID: 35319270.
- Strawn JR, Prakash A, Zhang Q, Pangallo BA, Stroud CE, Cai N, Findling RL. A randomized, placebo-controlled study of duloxetine for the treatment of children and adolescents with generalized anxiety disorder. J Am Acad Child Adolesc Psychiatry. 2015 Apr;54(4):283-93. doi: 10.1016/j.jaac.2015.01.008. Epub 2015 Jan 29. PMID: 25791145.
- Zarinara AR, Mohammadi MR, Hazrati N, Tabrizi M, Rezazadeh SA, Rezaie F, Akhondzadeh S. Venlafaxine versus methylphenidate in pediatric outpatients with attention deficit hyperactivity disorder: a randomized, double-blind comparison trial. Hum Psychopharmacol. 2010 Nov;25(7-8):530-5. doi: 10.1002/hup.1148. Epub 2010 Sep 22. PMID: 20860068.