Maryland Behavioral Health Integration in Pediatric Primary Care (MD BHIPP)

Managing Side Effects of Psychiatric Medications in Pediatric Primary Care: practical tips and clinical pearls

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Maryland Behavioral Health Integration in Pediatric Primary Care

1-855-MD-BHIPP (632-4477)

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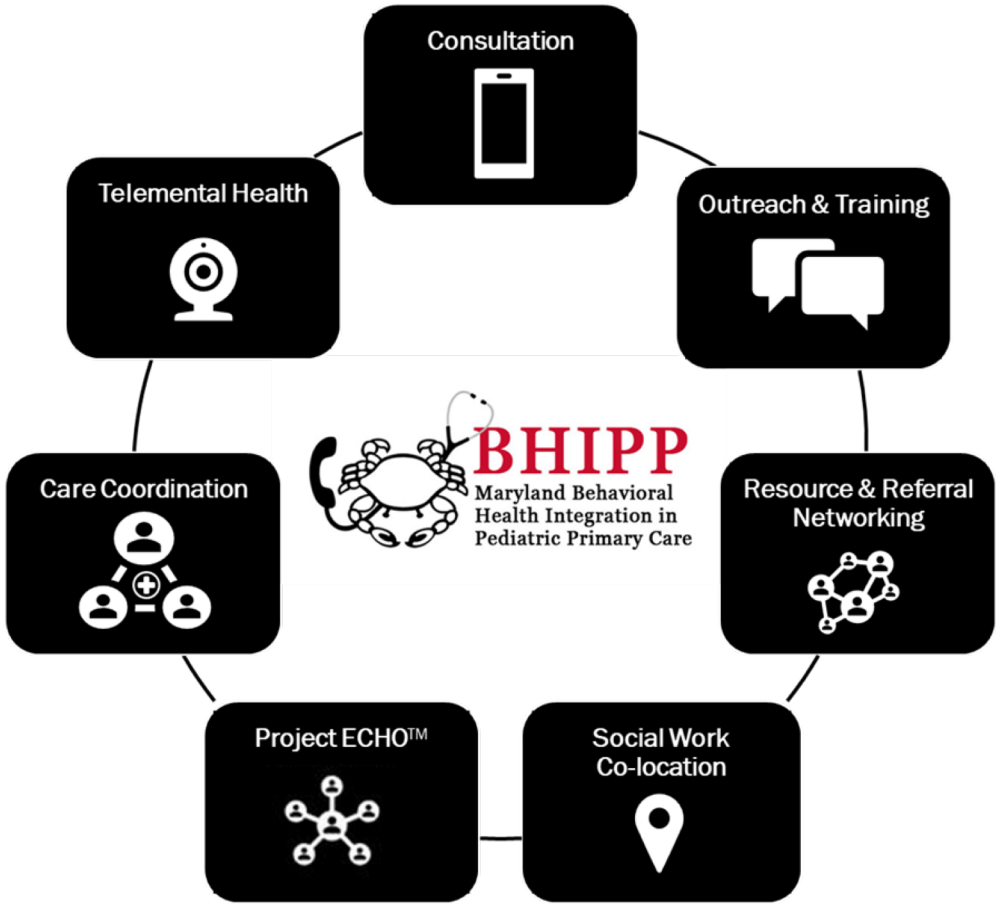
Who We Are – Maryland BHIPP



Offering support to pediatric primary care providers through free:

- Telephone consultation (855-MD-BHIPP)
- Resource & referral support
- Training & education
- Regionally specific social work co-location (Salisbury University and Morgan State University)
- Project ECHO®
- Direct Telemental health services
- Care coordination

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Partners & Funding

- BHIPP is supported by funding from the **Maryland Department of Health, Behavioral Health Administration** and operates as a collaboration between the **University of Maryland School of Medicine**, the **Johns Hopkins University School of Medicine**, **Salisbury University** and **Morgan State University**.

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Disclosures

- Mark Riddle- Employee of Johns Hopkins School of Medicine, receives funding BHIPP
- Sarah Edwards- Employee University of Maryland School of Medicine, receives funding for BHIPP

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Learning Objectives

In children and adolescents, be able to:

1. Identify and manage side effects of medications for ADHD
2. Identify and manage side effects of medications for anxiety and depression
3. Identify and manage side effects of other medications for psychiatric disorders

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The Side Effects Dilemma

- Too many medications
- Too many side effects
- Limited time
- Limited reimbursement

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Other Similar Dilemmas

- Number of Preparations for ADHD
  - About 20 for methylphenidate
  - Over 15 for amphetamine
- Psychiatry's Diagnostic and Statistical Manual (DSM)
- Anxiety example:
  - Separation, Specific, Social, Generalized, Panic
  - Possible symptoms—Panic has 14
  - How many symptoms needed
  - Age of onset
  - Duration of symptoms
  - Distress and Impairment

What To Do? Keep It Simple without Dumbing It Down

Reduce	Reduce number of medications needed to provide quality care
Prioritize	Prioritize medications with the best side effect profiles
Try 1st	Try first choice medication
Try 2nd	If needed, try second choice medication
Consider	If both fail, consider consult with BHIPP

Reducing Number & Prioritizing Medication

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The Problem: Too Many Meds

- There are **>110** psychotropic medications available for prescribing worldwide (see App for ECNP's "Neuroscience-based Nomenclature [NbN])"
- Most of these medications are FDA-approved for adults in the U.S.
- This large number of medications can be overwhelming, even for experienced specialists
- Thus, the proposed conceptual framework focuses on a ***small group of safe and effective medications***

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Conceptual Framework

Medications prioritized by:

- Safety
- Efficacy

Secondary priorities:

1. Prescriber comfort
   (i.e., FDA approval)
2. Convenience
   (i.e., once daily dosing)
3. Cost
   (i.e., generic available)

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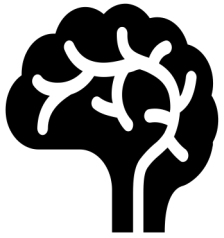
Conceptual Framework

Rationale



Group 1

ADHD: 2 stimulants, 2 alpha-2 adrenergic agonists, 1(2) NRIs

Anxiety and Depression: 3(4) SSRIs, 1 SNRI

Group 2

Psychosis, Mania, "Irritability in ASD": 6 SGAs, 1 TGA, lithium

Group 3

10 Other Medications

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Evidence of Efficacy

- There is no single “gold standard.”
- The FDA requires separation from placebo in 2 well-designed, randomized clinical trials.
- Because studies in youth are rare, the FDA sometimes accepts one high-quality study.
- This approach is used by the *GRADE Work Group* to evaluate treatments in youth.

Evidence of Safety

5 Parameters

FDA Approval in Youth

- Requires evidence of *short-term safety*

Sufficient Exposure (10+ Years on Market)

- Minimizes risk of *rare* adverse events

No Substantive FDA Boxed Warning

- Reduces likelihood of *serious* adverse event

Minimal Overdose Harm

- Reduces risk of *accidental/intentional harm*

No/Minimal Known Long-Term Risk

FDA and Adverse Effects (fluoxetine 10/21)

Boxed Warnings
- Suicidal thoughts and behaviors

Contraindications
- Serotonin syndrome with MAOIs, pimozide & thioridazine (QT prolongation)

Warnings and Precautions
- 14: all of considerable concern

Adverse Reactions
- 22: Most common ARs *(>5% and at least twice that of placebo)*

Drug Interactions
- MAOIs, drugs metabolized by 2D6, TCAs, CNS acting drugs, benzo's, APs, ACs, serotonergic drugs, drugs that interfere with hemostasis, protein bound

- Drugs@FDA: www.accessdata.fda.gov

Prozac (fluoxetine) W&Ps 1 & 2

• *Suicidal Thoughts and Behaviors in Children, Adolescents, and Young Adults*: Monitor for clinical worsening and suicidal thinking and behavior (5.1)

• *Serotonin Syndrome*: Serotonin syndrome has been reported with SSRIs and SNRIs, including PROZAC, both when taken alone, but especially when co-administered with other serotonergic agents (including *triptans*, tricyclic antidepressants, fentanyl, *lithium*, tramadol, *tryptophan*, *buspirone*, *amphetamines*, and *St. John's Wort*).

- If such symptoms occur, discontinue PROZAC and initiate supportive treatment.
- If concomitant use of PROZAC with other serotonergic drugs is clinically warranted, patients should be made aware of a potential increased risk for serotonin syndrome, particularly during treatment initiation and dose increases (5.2)

Antidepressants & “Suicidality”

“Suicidality” = ideation &/or attempt

FDA 2006 (4,300): 4% vs 2% = 2%

Larger data set (5,000) = 0.7%(1/133)

Largest data set (6,000) = 0.9% (N.S.)

Conclusion: Real in about 1%

- Probably due too behavioral activation
- *Monitoring = Safety*
- *NOTE: due to paroxetine & venlafaxine?*

Serotonin Syndrome*

GI: nausea, vomiting, diarrhea

Mental Status: agitation, delirium, hallucinations, coma

Autonomic Instability: tachycardia, labile blood pressure, diaphoresis, hyperthermia, flushing, dizziness

Neuromuscular: tremor, hyperreflexia, rigidity, myoclonus, hyperreflexia, incoordination

*5HTP supplements and tryptans for migraines common causative agents

Prozac (fluoxetine) W&Ps 3 to 7

- *Allergic Reactions and Rash*: Discontinue upon appearance of rash or allergic phenomena (5.3)
- *Activation of Mania/Hypomania*: Screen for Bipolar Disorder and monitor for mania/hypomania (5.4)
- *Seizures*: Use cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold (5.5)
- *Altered Appetite and Weight*: Significant weight loss has occurred (5.6)
- *Abnormal Bleeding*: May increase the risk of bleeding. Use with NSAIDs, aspirin, warfarin, or other drugs that affect coagulation may potentiate the risk of gastrointestinal or other bleeding (5.7)

Prozac (fluoxetine) W&Ps 8 to 12

- *Angle-Closure Glaucoma*: Angle-closure glaucoma has occurred in patients with untreated anatomically narrow angles treated with antidepressants (5.8)
- *Hyponatremia*: Has been reported with PROZAC in association with syndrome of inappropriate antidiuretic hormone (SIADH). Consider discontinuing if symptomatic hyponatremia occurs (5.9)
- *Anxiety and Insomnia*: May occur (5.10)
- *QT Prolongation*: QT prolongation and ventricular arrhythmia including Torsades de Pointes have been reported with PROZAC use. Use with caution in conditions that predispose to arrhythmias or increased fluoxetine exposure. Use cautiously in patients with risk factors for QT prolongation (4.2, 5.11)
- *Potential for Cognitive and Motor Impairment*: Has potential to impair judgment, thinking, and motor skills. Use caution when operating machinery (5.13)

Prozac (fluoxetine) W&Ps 13 & 14

- *Long Half-Life*: Changes in dose will not be fully reflected in plasma for several weeks (5.14)
- XXXXXXXXXXXPROZAC and Olanzapine in Combination: When using PROZAC and olanzapine in combination, also refer to the Warnings and Precautions section of the package insert for Symbyax (5.16)
- *Sexual Dysfunction*: PROZAC may cause symptoms of sexual dysfunction (5.17)

Prozac (fluoxetine) Most Common Adverse Reactions

Most common adverse reactions (≥5% and at least twice that for placebo) associated with:

- *Major Depressive Disorder, Obsessive Compulsive Disorder, Bulimia, and Panic Disorder*: abnormal dreams, abnormal ejaculation, anorexia, anxiety, asthenia, diarrhea, dry mouth, dyspepsia, flu syndrome, impotence, insomnia, libido decreased, nausea, nervousness, pharyngitis, rash, sinusitis, somnolence, sweating, tremor, vasodilatation, and yawn (6.1)

Discontinuation Syndrome*

- Flu-like symptoms
- GI symptoms – nausea, vomiting, diarrhea

- Dizziness, vertigo
- Tingling/numbness

- Sleep disruption
- Anxiety, agitation
- Irritability, low mood

***Taper, except fluoxetine**

Group 1 Medications
Anxiety Disorders

Drug (mode of action)	Indication(s)	FDA Approval/ Approved Age	Level of Evidence	Generic
Fluoxetine (SSRI)	ANX OCD	No Yes; ≥ 7	B A	Yes
Sertraline (SSRI)	ANX OCD	No Yes; ≥ 6	B A	Yes
Fluvoxamine (SSRI)	ANX OCD	No Yes; ≥ 8	B A	Yes
Duloxetine (SNRI)	Generalized Anxiety	Yes (> 6)	A/B	Yes

Group 1 Medications
Major Depressive Disorder (MDD)

Drug (mode of action)	Indication(s)	FDA Approval/ Approved Age	Level of Evidence	Generic
Fluoxetine (SSRI)	MDD	Yes; ≥ 8	A	Yes
Escitalopram (SSRI)	MDD	Yes; ≥ 12	A	Yes

SSRIs

How Risk is Presented

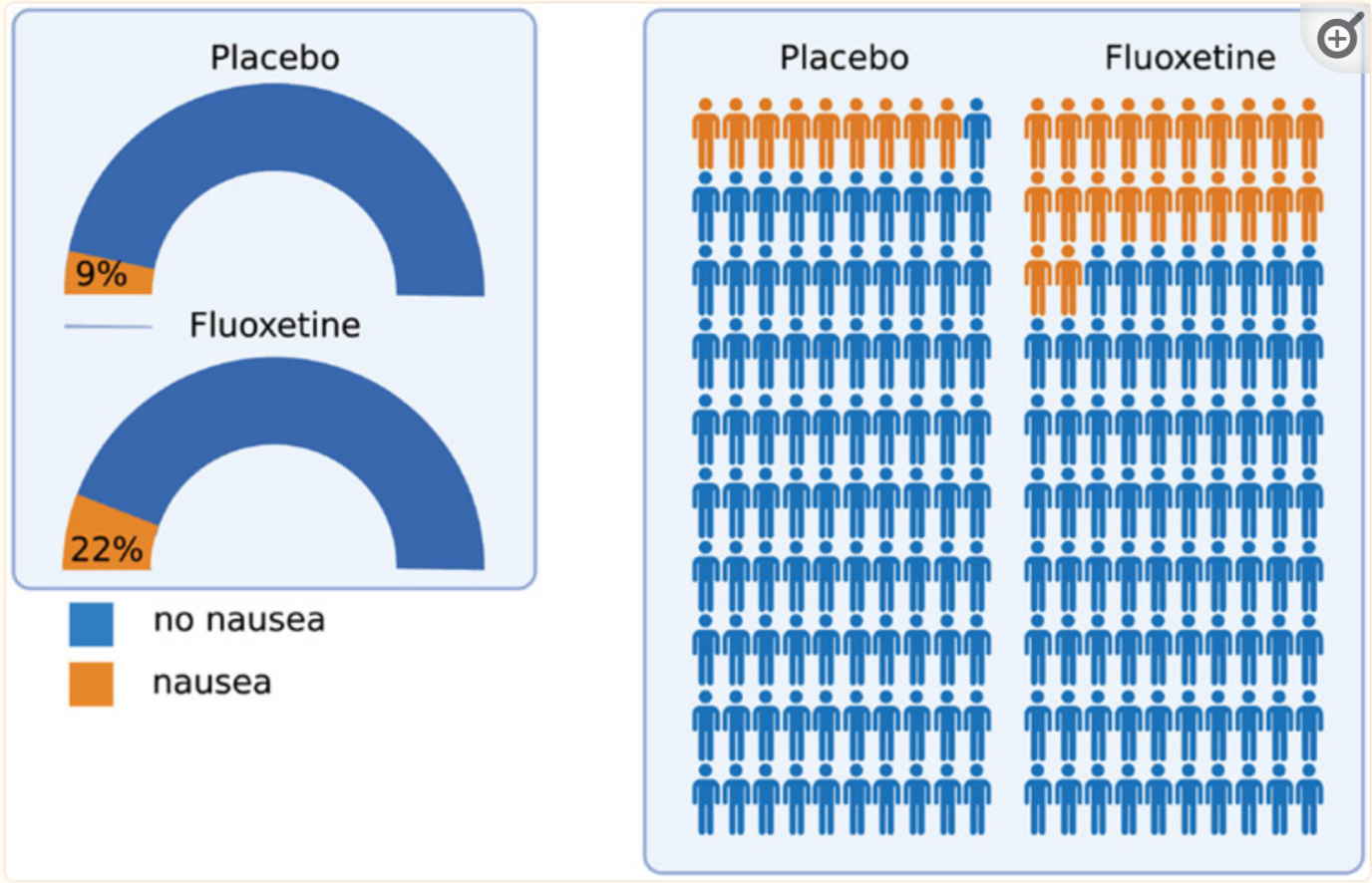
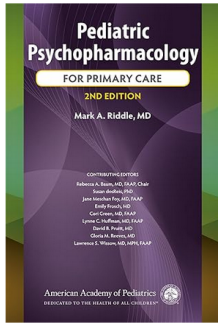


FIGURE 2

Alternative Approaches to Visualizing Adverse Effects. In contrast to presenting relative rates, odds ratio, or bar graphs, adverse effects can be visually presented relative to the population of antidepressant-treated patients and the comparison group to provide more context. Modified gauges (left) and a pictogram (right) show the incidence of nausea (based on rates in the package insert) for fluoxetine-treated patients across registration trials. *Figure created using* BioRender.com

Strawn et al, Pharmacotherapy, 2023

Talking with Patients and Family about Safety



- Many healthy children do not have side effects of SSRIs
- SE are reversible if the medication is decreased or discontinued
- Most common SE are upset stomachache/nausea, which occur soon after med is started/increased. Often subsides in a few days
- Agitation or behavioral activation can be common with dosage increases, usually subsides over a few days
- Less common SE are disrupted sleep. Daytime sleepiness, fatigue, or tremor
- Adolescents may have increased sweating, decreased sexual desire or delayed orgasm
- Suicidal thoughts/behaviors can emerge during recovery from depression; 1 in 100 to 150 patients taking med vs placebo develop; education and safety plan

Riddle, Psychopharm book, 3rd edition

Main Side Effects of SSRIs

EARLY-EMERGING SIDE EFFECTS

GI Symptoms, Insomnia, Tiredness, Activation

PERSISTENT OR LATE-EMERGING ADVERSE EFFECTS

Weight gain, Xerostomia, Sexual Dysfunction,

Strawn et al, Pharmacotherapy, 2023

Reversible Side Effects of SSRIs

- GI discomfort, nausea, → Take with food, take before bed
- Insomnia → Take in the morning
- Daytime sedation, tiredness → Take in evening
- Behavioral activation……suicidality → Start low, go slow, lower dose, slow titration
  - more common in younger children
  - agitation, restlessness, insomnia, impulsivity
  - behavioral disinhibition

Strawn et al, Pharmacotherapy, 2023

Antidepressant-associated weight gain

- For SSRI-treated youth, weight gain can emerge early or late and may persist.
- The two SSRIs associated with the most weight gain in prospective studies of youth with anxiety and depressive disorders are paroxetine and citalopram.

Strawn et al, Pharmacotherapy, 2023

Effect of antidepressant drugs on body weight

ADULTS

DRUG	EFFECT ON WEIGHT
Monoamine oxidase inhibitors (irreversible type)	Weight gain likely in short term (< 6 months) and long term (≥ 1 year)
Tricyclic compounds	Weight gain likely in short term and long term
Selective serotonin reuptake inhibitors (SSRIs) other than paroxetine	Weight gain in short term less likely Weight gain in long term possible, but evidence is varied
Paroxetine	Weight gain in short and long term more likely than for other SSRIs
Nefazodone	Likely to have no effect on weight
Bupropion	Likely to cause weight loss
Mirtazapine	More likely than placebo to cause weight gain in short term, but less likely than tricyclics
Venlafaxine	Likely to have no effect on weight

Deshmukh and Franco, 2003, Cleveland Clinic J of Med

What to do…

- Monitor diet and exercise
- Patients may benefit from a nutritional consultation
- Maintaining a food diary and behavioral techniques such as increasing meal frequency, smaller meals, or decreasing the pace of eating can help.
- Switching to another drug with a lower risk of weight gain is an alternative approach, although this carries a risk of loss of clinical effect.
- In adults: addition of another agent such as a stimulant (methylphenidate, amphetamines), bupropion, may help diminish weight gain.

Deshmukh and Franco, 2003, Cleveland Clinic J of Med

Dry Mouth
Xerostomia

- Water, sugarless candy, chewing gum
- Avoid caffeine/alcohol,
- Use non-alcoholic mouth wash

We must ask about Sexual Side Effects!

Have you experienced a change in libido (sexual desire, thoughts, interest)?

Have you noticed a change in orgasm since starting the medication, such as a delayed orgasm or not able to achieve one?

Have you had difficulties obtaining an erection?

Levine and McGlinchey 2014 Pediatrics

If Experiencing Sexual Side Effects:

Low sexual desire: switching to a non-serotoninergic drug, lowering the dose, or associating bupropion

Unwanted orgasm delayal or anorgasmia: dose reduction, “weekend holiday”, or switching to a non-serotoninergic drug

Erectile dysfunction: switching to a non-serotoninergic drug

Montejo, et al. 2019, J Clinical Medicine

ADHD Medications
Stimulants

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Group 1 Medications
ADHD

Drug (mode of action)	Indication	FDA Approval/ Approved Age	Level of Evidence	Generic
Methylphenidate (stimulant)	ADHD	Yes; ≥ 6	A	Yes
Amphetamine (stimulant)	ADHD	Yes; ≥ 6 (3)	A	Yes
Guanfacine (α-2 adren. agonist)	ADHD	Yes; ≥ 6	A	Yes
Clonidine (α-2 adren. agonist)	ADHD	Yes; ≥ 6	A	Yes
Atomoxetine (NRI)	ADHD	Yes; ≥ 6	A	Yes

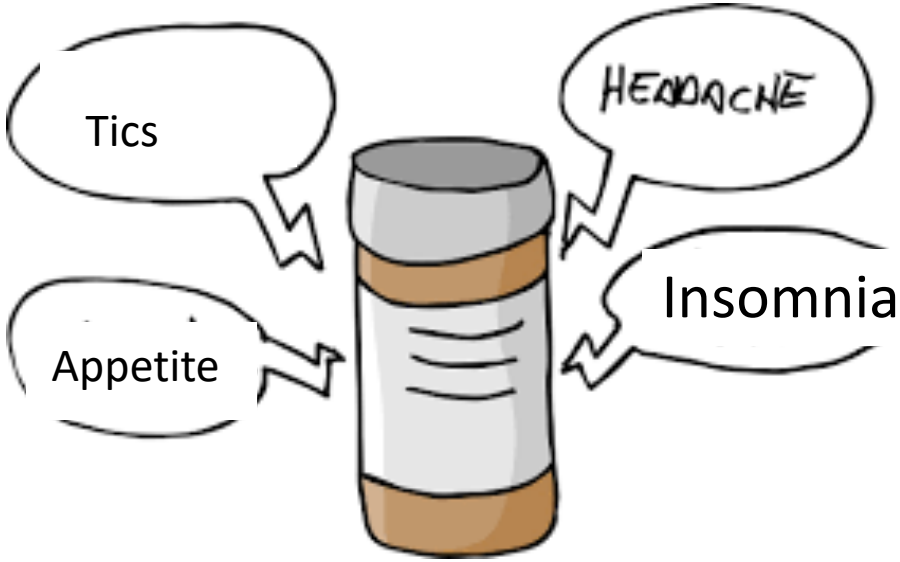
Stimulant Delivery Systems

Preparation	Time (hrs)	Methylphenidate	Amphetamine
▪ IR	3-4 4-6	Ritalin Focalin	Adderall/EVEKEO ZENZEDI (d-amphetamine)
▪ Pulse	7-8	Metadate ER APTENSIA XR ADHANSIA XR	Dexedrine Spansule MYDAYIS
▪ Pearls	8-12	Metadate CD Ritalin LA FOCALIN XR JORNAY PM	Adderall XR
▪ Pump	≤12	Concerta	
▪ Modified IR	≤12		VYVANSE
▪ Liquid/Chewable	3-5	Methylin/Methylphenidate	PROCENTRA/VYVANSE
▪ Disintegrating	4-6		EVEKEO ODT
▪ Liquid Susp.	8-12	QUILLIVANT XR	DYANAVEL XR ADZENYS ER
▪ Chewable/Disint	8-12	QUILLICHEW ER/CONTEMPLA XR-ODT	--- /ADZENYS XR-ODT
▪ Patch	≤12	DAYTRANA	

Main Side Effects of Stimulants

Most Common

- Abdominal pain
- Appetite suppression
- Difficulty falling asleep



Less Common

- Growth suppression (recent FDA precaution)
- Dysphoria (preschoolers)
- Behavioral/cognitive constriction (high dose)
- Tics
- Hemodynamic (common and minimal)
- Cardiac (rare if structural abnormality)

Possible Stimulant Adverse Effects

- Spacey/ too serious too quiet → Adjust dose, switch
- Rebound irritability → Add short-acting

- Tics → Risk/Benefit
  Lower dose
  Add alpha-agonist

- GI Upset → Eat before medication
- Headache → Hydration, food, switch

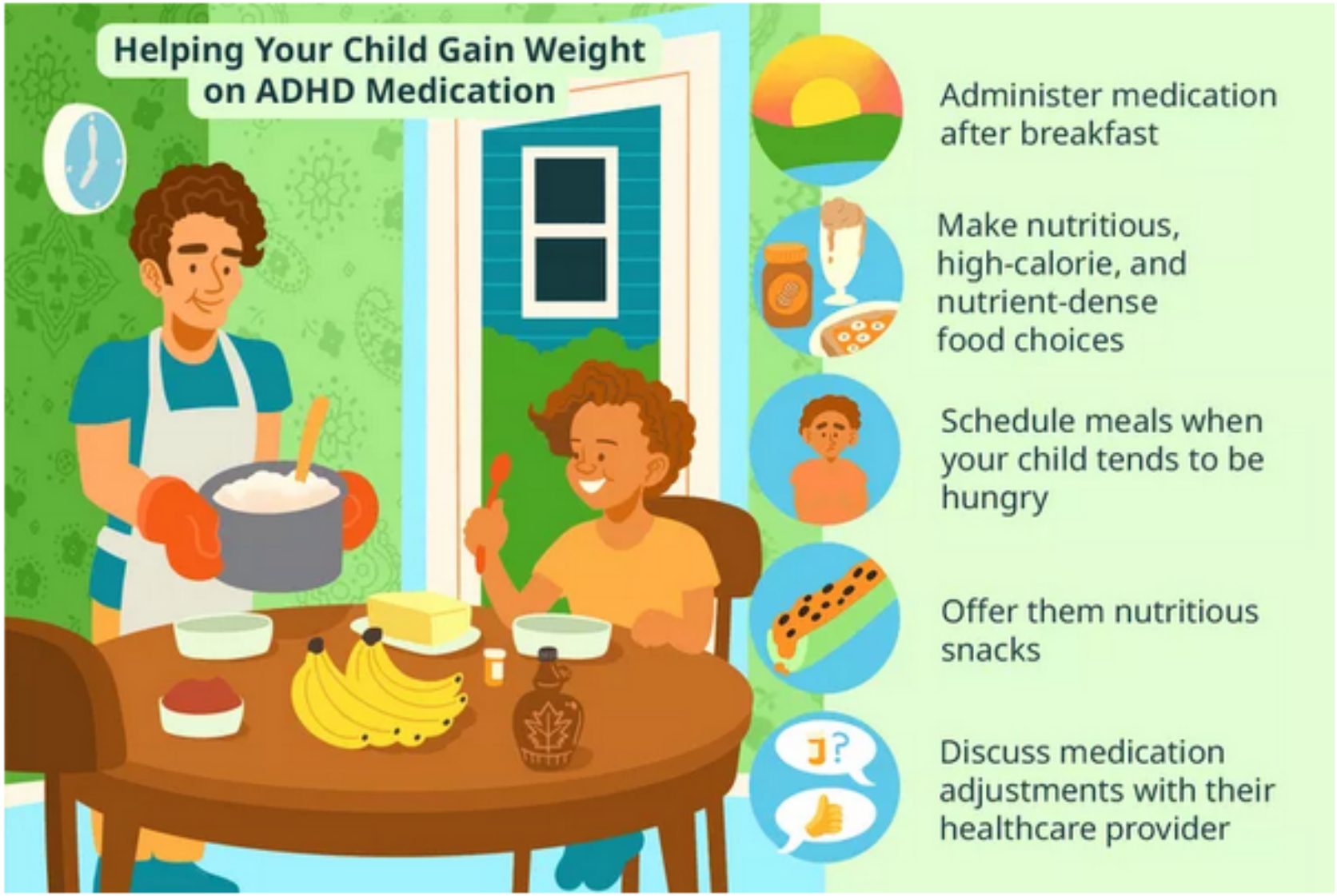
Preschoolers

- PATS Study: simulants work in this age group, but not as well and young kids have more adverse effects
- Adverse events most frequently reported in the study:
  - Appetite decrease
  - Emotional outbursts & irritability
  - Difficulty falling asleep

Decreased Appetite and Weight Loss Stimulants

Decreased Appetite / Weight Loss

- Initial loss, typically resolves
- Consider drug holidays



Verywell / Ellen Lindner

Breakfast

- Add butter to things like oatmeal or grits.
- Add peanut butter to fruit (apples and bananas)
- Add cheese to eggs,
  use whole milk
- All drinks should be AFTER they finish eating.

Lunch and Dinner

- Add butter to things like pasta, macaroni and cheese, potatoes, & vegetables.
- Add cheese to dishes or even a little extra cheese.
- Use regular salad dressing or cheese sauce on vegetables.
- All drinks should be AFTER they finish eating.

Snacks

- Expect that your child may be able to eat up to 3 snacks day.
- Regular yogurt and cheese are good snacks.
- Fruit and vegetables can have peanut butter, salad dressing or hummus with it.

Drinks

- Drink whole milk- no 1 or 2% or skim.
- You can add 1-2 spoonfuls of whipping cream to milk
- Extra supplements like Carnation Instant Breakfast or Pediasure. See website for flavor, types and recipes. https://www.carnationbreakfastessentials.com/
- DO NOT give juice or soda- this is bad for their teeth and just contains sugar.
- You can also try making shakes
- Milk or yogurt with fruit or peanut butter can be great combinations.

EACH NUTRIENT-PACKED BREAKFAST DRINK PROVIDES

When prepared as directed with 1 cup of skim milk

Source-USDA FoodData Central: One large egg has 6.3 g protein. One 5.3 oz cup of Greek Yogurt contains 141 mg calcium. One 8 fl oz glass of skim milk contains 2.9 mcg vitamin D. One medium orange has 70 mg vitamin C.

As much

PROTEIN

AS TWO

large eggs

As much

CALCIUM

AS THREE

5.3 oz cups of Greek Yogurt

As much

VITAMIN D

AS THREE

8 fl oz glasses of milk

As much

VITAMIN C

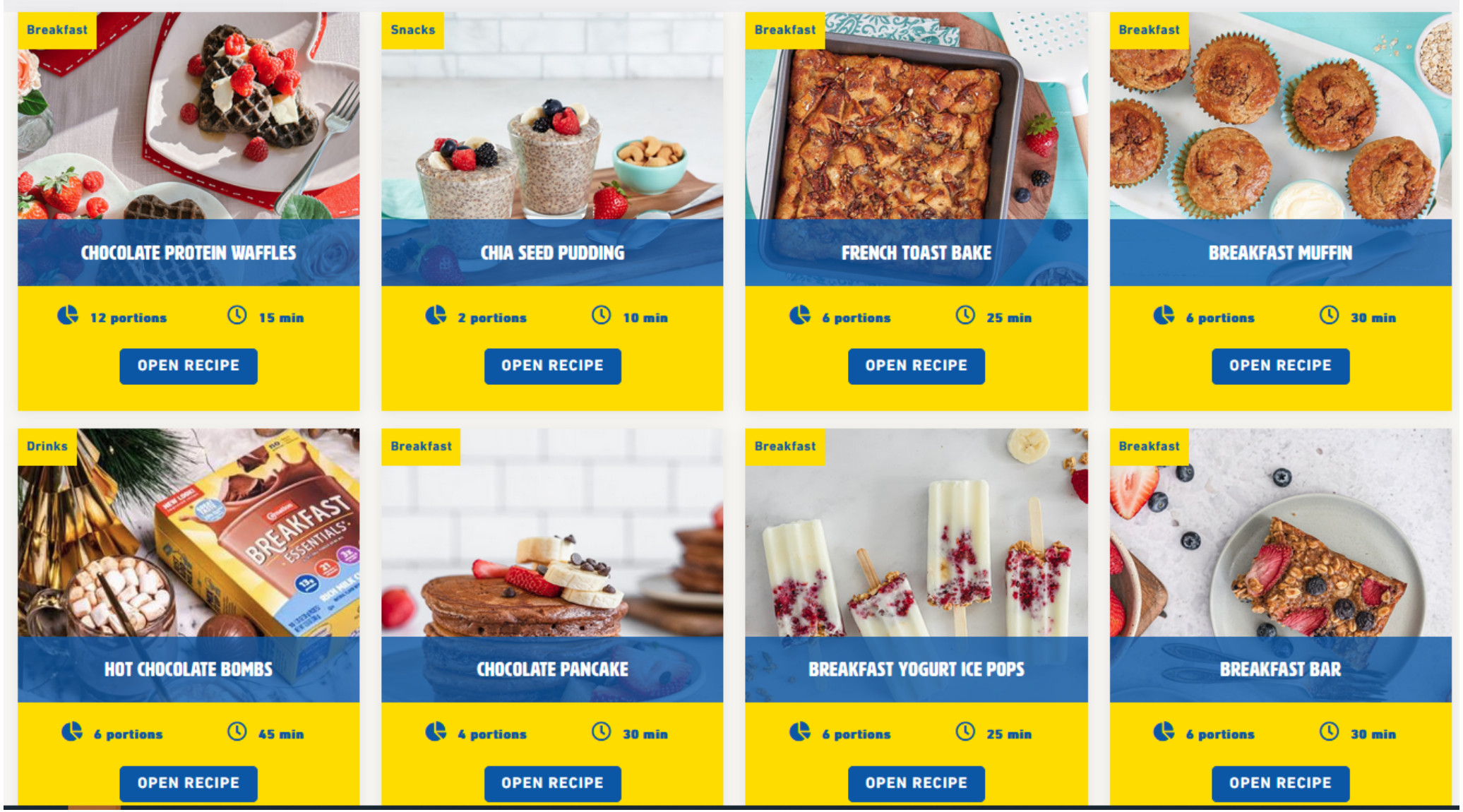
AS ONE

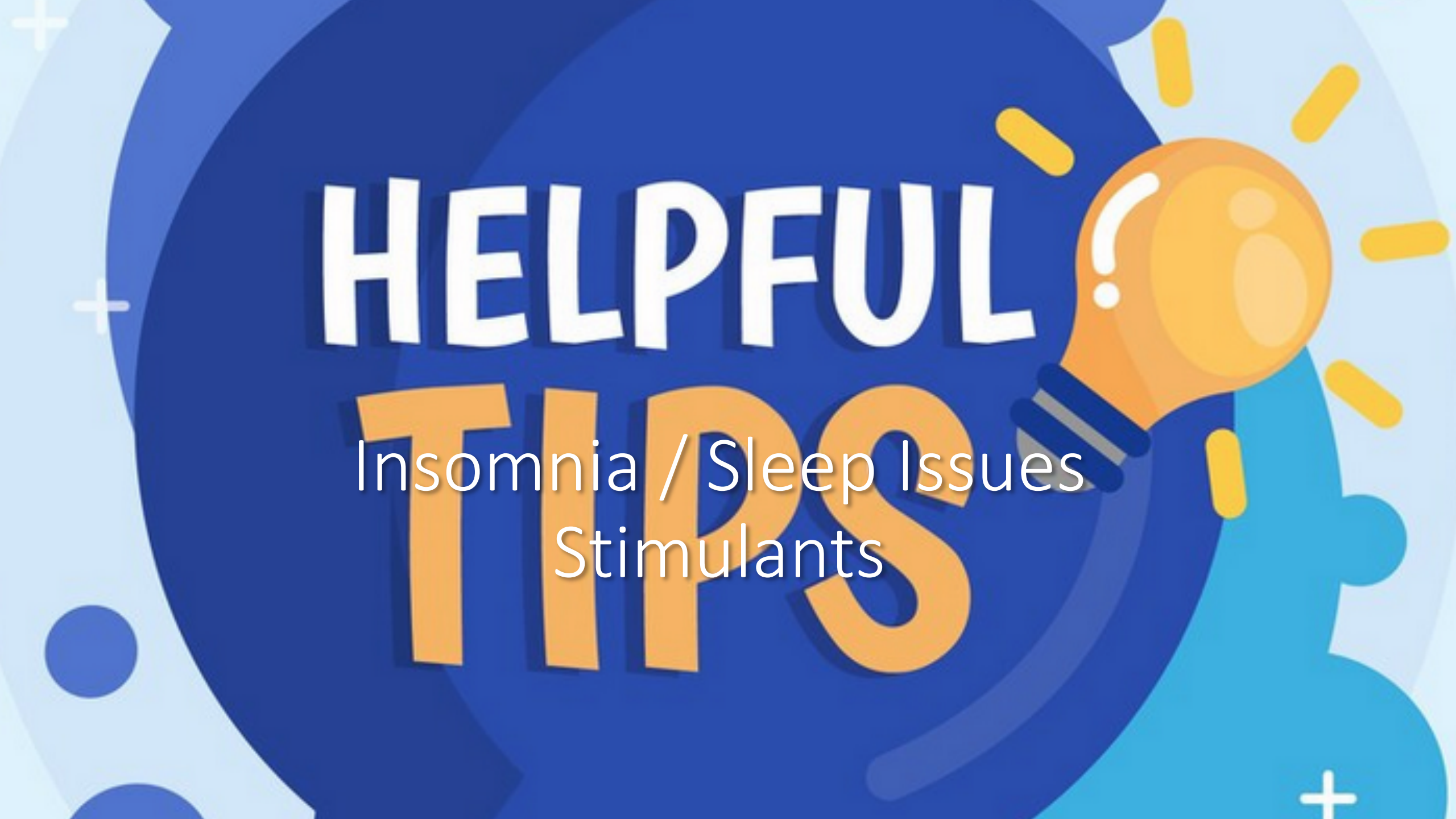
medium orange

Flavors!

Chocolate, Cinnabon, Coconut Caramel
Frosted Flakes, Rice Krispies Treats, Thin Mints
Cookie N’ Crème, Vanilla, Strawberry

Recipes- Mix it in!





Insomnia / Sleep Issues
Stimulants

Insomnia

- Consider changing medication timing/dosage
- Sleep Routine
- No electronics 1 hour before bed
- White noise machine or soft music for relaxation

Insomnia
Teens & Screens

- Harm reduction approach to screens
- Passive use better than active use
- Smaller screen, less blue light
- Blue blocking glasses, or app

ADHD Medications
Alpha-Agonists

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Alpha-2 Adrenergic Agonists: Guanfacine and Clonidine

Developed as antihypertensives

Receptor subtypes:

- A prefrontal (attention, inhibition, memory)
- B baroreceptor (blood pressure & pulse)
- C striatum (activity?, stress response?)

Guanfacine: **specific** to A subtype

Clonidine: **nonspecific**: all 3 subtypes

Dosing α-Adrenergic Agonists

	Guanfacine	Clonidine
Start	0.5-1.0*	0.05-0.1
Wkly increase	0.5-1.0	0.05-0.1
Max/day	4.0 or 7.0	0.4
Duration	24 hrs**	12 hrs (bid)**

*Guanfacine dose is 10x higher

** for long-acting preps Intuniv and Kapvay

Guanfacine (Intuniv) Adverse Events

Most Common*:

- Somnolence
- Fatigue
- Lethargy
- Nausea
- Hypotension

Clonidine (Kapvay) Adverse Events

Most Common*:

- Somnolence
- Fatigue
- Insomnia
- Nightmares, Irritability
- Others (emotional disorder, dry mouth)

Warnings & Precautions for both:

- Hypotension, bradycardia, syncope
- Sedation and somnolence
- Cardiac conduction abnormalities (worsen sinus node dysfunction and atrioventricular block)
- Abrupt withdrawal can cause rebound hypertension

* >5% and at least twice placebo rate (FDA definition)

Alpha-Agonists

Somnolence and Lethargy

- Timing of medications- use to your advantage
- Can give the long acting in the morning or evening
- Can lessen with time

Other Psychotropic Medications

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Call BHIPP!

Citations

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