Challenges in Pediatric Population Management of ADHD

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Relevant Financial Relationship Disclosure

No one in control of the content of this activity has a relevant financial relationship with an ineligible company as defined by the Standards of Integrity and Independence in Accredited Continuing Education definition of an ineligible company.

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Abbreviations

- ADD - Attention Deficit Disorder
- ADHD - Attention Deficit Hyperactivity Disorder
- AAP - American Academy of Pediatrics
- ASD - Autism Spectrum Disorder
- CBT - Cognitive Behavioral Therapy
- CD - Conduct Disorder
- DSM - Diagnostic and Statistical Manual of Mental Disorders
- MAOI - Monoamine Oxidase Inhibitor
- ODD - Oppositional Defiant Disorder
- PTBM - Parent Training in Behavior Management
- SUD - Substance Use Disorder

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Objectives

- Review diagnostic criteria and describe how the presentation of ADHD changes over the age spectrum
- Highlight common adverse events of pharmacotherapy (stimulant and non-stimulant) and their implications
- Evaluate and design pharmacologic and non-pharmacologic treatment regimens based on patient-specific parameters such as age, comorbid conditions, and avoidance of side effects
- Identify and discuss structural and attitudinal barriers to care
- Explore alternative pharmacotherapies as workaround to medication shortages
- Improving long-term care outcomes through Multimodal Treatment of ADHD (MTA)

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Part 1 – Presented by Sara Ghaderi

Review diagnostic criteria and describe how the presentation of ADHD changes over the age spectrum → Highlight common adverse events of pharmacotherapy (stimulant and non-stimulant) and their implications → Evaluate and design pharmacologic and non-pharmacologic treatment regimens based on patient-specific parameters such as age, comorbid conditions, and avoidance of side effects

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Attention Deficit Hyperactivity Disorder (ADHD)

- Neurodevelopmental disorder characterized by difficulty paying attention or managing impulsive behaviors
- Previously two different diagnoses: Attention Deficit Disorder (ADD) and Attention Deficit Hyperactivity Disorder (ADHD)
- The DSM IV combined them into one disorder (ADHD) with three subtypes:
  - Predominantly inattentive
  - Predominantly hyperactive
  - Combined type
- While ADHD affects both children & adults, it is often diagnosed in childhood

Attention Deficit Hyperactivity Disorder. StatPearls.

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ADHD Diagnostic Criteria (DSM-5)

- Persistent signs/symptoms of inattention and/or hyperactivity/impulsivity that interfere with individual's daily functioning or development
  - At least **6 months** with inattention or hyperactivity/impulsivity symptoms
    - At least **6 symptoms** are required for children and adolescents **up to age 16**
    - At least **5 symptoms** are required for ages **17 and up**
- Several symptoms present **before** the age of **12**
- Several symptoms present in **2 or more** settings (*i.e.*, school, home, or other social occasions)
- The negative impact of symptoms on social/academic functioning is **clear** and **evident**
- Symptoms are **not** due to another mental condition (*i.e.* mood disorder, substance intoxication or withdrawal)

Can Fam Physician. 2020;66(10):732-736.

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ADHD Symptoms

Inattention symptoms

- Fail to pay attention to details or make careless mistakes
- Difficulty maintaining attention to activities or tasks
- Do not appear to listen when directly addressed, even in the absence of obvious sources of distraction
- Fail to finish tasks or follow through on instructions
- Trouble organizing/managing tasks or activities
- Avoid/dislike tasks or activities that require prolonged mental effort
- Lose items often
- Distracted easily by external stimuli
- Forget routine activities

Hyperactivity/impulsivity symptoms

- Fidget or squirm when seated
- Unable to remain seated when required/expected to
- Run about or climb objects inappropriately
- Unable to remain quiet when playing or participating in leisure activities
- Unable to remain still for an extended period of time
- Talk excessively
- Complete others' sentences or speak/answer before a question is fully stated
- Unable to wait for their turn
- Interrupt, intrude, or take over others' conversations, activities, or objects

Can Fam Physician. 2020;66(10):732-736.

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Prevalence & Trends

- In 2022, 11.4% of U.S. children aged 3–17 years (7.1 million) had ever been diagnosed with ADHD by a health care provider according to parent report
- The prevalence of children ever diagnosed with ADHD increased by age:
  - 2.4% of children aged 3–5 years (274,000)
  - 11.5% of children aged 6–11 years (2.8 million)
  - 15.5% of adolescents aged 12–17 years (4.0 million)
- The prevalence of diagnosed ADHD varies by socio-demographic factors, it is more common in:
  - Young males
  - Children living in lower-income households
  - Children with public health insurance
  - Children living in rural areas

J Clin Child Adolesc Psychol. 2024;53(3):343-360

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Risk Factors

Environment factors
- Gestational & perinatal conditions (premature birth, decreased docosahexaenoic acid (DHA) during brain development)
- Heavy metals

Sleep disorders

Genetic factors
- Brain-derived neurotrophic factor (BDNF)
- Dopamine transporter (DAT)

Changes in brain structure & function

J Pers Med. 2021;11(3):166.

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Age Groups

Preschool-aged children	Elementary to middle school-aged children	Adolescents
• Ages 4 – 5	• Ages 6 – 11	• Ages 12 – 18

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Presentation Over Age Continuum

- Symptoms of hyperactivity & impulsivity can appear as early as age 3 while inattention symptoms seem to appear later in childhood (around ages 6-12)
- While hyperactivity may improve with age, inattentiveness and impulsivity can often persist into adolescence and adulthood
- ADHD persists into adolescence in as many as **85%** of patients
- ADHD persists into adulthood in as many as **60%** of patients
- Comorbidities like anxiety and depression are more likely to develop during adolescence

Pediatrics. 2019;144(4):e20192528.

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Gender Differences

Boys are more than **twice** as likely as girls to receive a diagnosis of ADHD

Girls had a higher prevalence of anxiety or depression

Boys more often had behavioral or conduct problems or autism spectrum disorder

Boys are more likely to exhibit externalizing conditions like oppositional defiant disorder or conduct disorder

Pediatrics. 2019;144(4):e20192528.

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Treatment Based on Age Groups

Preschool-aged children	Elementary to middle school-aged children	Adolescents
PTBM &/or behavioral classroom interventions is first line Consider methylphenidate (Nonstimulants do not have FDA approval in this age group)	FDA approved medications along with PTBM &/or behavioral classroom interventions (Stronger evidence for stimulants than nonstimulants)	FDA approved medications with the adolescent's assent Encourage prescribing of PTBM &/or behavioral classroom interventions

There is insufficient evidence to recommend diagnosis or treatment for children younger than 4 years (other than PTBM, which does not require a diagnosis to be applied)

Pediatrics. 2019;144(4):e20192528.

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ADHD Treatment

Pharmacologic

- Stimulants:
  - Amphetamine formulations
  - Methylphenidate formulations
- Nonstimulants:
  - Selective norepinephrine reuptake inhibitors
  - Centrally acting alpha-2 agonists

Nonpharmacologic

- Parent training in behavior management (PTBM)
- Behavioral classroom interventions
- Cognitive Behavioral Therapy (CBT)
- Nutrition and supplements

Pediatrics. 2024;153(4):e2024065787

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Stimulant Pharmacotherapy Options

- **Amphetamine formulations**
  - Long acting:
    - Mixed amphetamine salts (Adderall XR®, Mydaysis®)
    - Amphetamine (Adzenys XR-ODT®, Dyanavel® XR)
    - Dextroamphetamine (Dexedrine Spansule®)
    - Lisdexamefetamine dimesylate (Vyvanse®)
  - Short acting:
    - Mixed amphetamine salts (Adderall®)
    - Amphetamine sulfate (Evekeo®)
    - Dextroamphetamine (Procentra®, Zenzedi®)
- **Methylphenidate formulations**
  - Long acting:
    - Methylphenidate (Concerta®, Daytrana®, Ritalin® LA)
    - Dexmethylphenidate (Focalin® XR)
    - Serdexmethylphenidate/Dexmethyl-phenidate (Azstarys®)
  - Short acting:
    - Methylphenidate (Ritalin®)
    - Dexmethylphenidate (Focalin®)

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Nonstimulant Pharmacotherapy Options

- **Selective norepinephrine reuptake inhibitors**
  - Atomoxetine (Strattera®)
  - Viloxazine (Qelbree®)
- **Centrally acting alpha-2 agonists**
  - Guanfacine (Intuniv®)
  - Clonidine (Kapvay®)

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Stimulants - Overview

Medication	Mechanism of Action	Side Effects	Warnings
Amphetamine	Promote release of catecholamines (primarily dopamine and norepinephrine) from their storage sites in the presynaptic nerve terminals	• Abdominal pain • Anorexia • Decreased appetite • Insomnia • Nausea • Vomiting	• Cardiovascular events • Growth suppression • Psychiatric/behavioral effects • Serotonin syndrome
Methylphenidate	Blocks the reuptake of norepinephrine and dopamine into presynaptic neurons; appears to stimulate the cerebral cortex and subcortical structures similar to amphetamines	• Decreased appetite • Nausea • Xerostomia • Headache • Insomnia • Irritability	• Cardiovascular events • Growth suppression • Priapism • Psychiatric/behavioral effects

Pediatrics. 2019;144(4):e20192528. Adderall. Package insert. Shire US Inc; 2013. Concerta. Package insert. ALZA Corporation; 2007.

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Stimulant Side Effects & Monitoring

Side Effects	Description
Cardiovascular events	Increased heart rate and blood pressure have been observed Stimulant medications have not been shown to increase the risk of sudden cardiac death in children
	Clinicians should routinely monitor **heart rate** and **blood pressure** Screen for pre-existing cardiac disease prior to initiation of stimulants
Psychiatric/ behavioral effects	Although rare, new onset or exacerbation of psychosis or mania symptoms such as delusion thinking, auditory and visual hallucinations may occur at any age
	Screening for psychiatric conditions prior to stimulant initiation may help to prevent new onset psychosis or mania and exacerbation of psychotic or manic symptoms
Serotonin syndrome	May occur when amphetamine is used in combination with other serotonergic agents in all ages Early symptoms include tachycardia, shivering, diarrhea, diaphoresis, muscle cramps, agitation, and increased body temperature; later symptoms are usually hypertension, hyperthermia, hyperreflexia, delirium, tremors, and rigidity
	Use caution if patient on other drugs that affect the serotonergic neurotransmitter system (*i.e.*, SSRIs, SNRIS)

Pediatrics. 2019;144(4):e20192528. *N Engl J Med*. 2019;380(12):1128-1138.

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Stimulant Side Effects & Monitoring (continued)

Side Effects	Description
Growth suppression	Decreased height and weight have been described in children on stimulants, more consistently noted on higher doses of stimulants
	Monitor **height** and **weight** regularly Discontinuation of stimulant therapy ("drug holidays") during school breaks may be considered in pediatric patients who are showing inadequate growth while on treatment
Decreased appetite	A meta-analysis found that stimulants significantly suppressed appetite
	Give meal 30-60 minutes prior to dose of stimulant
Insomnia	Sleep disturbance have commonly been indicated as a side effect of stimulant medications
	Initiate melatonin or alpha-2 agonist at bedtime

Pediatrics. 2019;144(4):e20192528. *N Engl J Med*. 2019;380(12):1128-1138. *Pediatrics*. 2024;153(4):e2024065787.

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Stimulants – Counseling/Clinical Pearls

- Take longer acting stimulants early in day to prevent insomnia (*i.e.*, Adderall XR®)
- Time administration so that medication starts working when needed (*i.e.*, give prior to school)
- Consider adding on short-acting agents when symptom coverage is still needed past long-acting medication effect
- When initiating stimulant therapy, the American Academy of Pediatrics (AAP) guideline recommends starting at a low dose and titrating up until an optimal dose is achieved
- Inform parents that their child's appetite may be suppressed
- For young children, parental discretion should be used regarding storage of these medications

Pediatrics. 2019;144(4):e20192528.

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Stimulants – Diversion Concern

- Prior to initiating stimulants in newly diagnosed adolescents, clinicians should assess the patient for symptoms of substance use
- In adolescents, SUD is common in those who also have a conduct disorder
- Another concern regarding adolescents is diversion of stimulant medication
- Frequent monitoring of medication is critical, as stimulants have a higher potential for misuse or diversion in the middle school or high school environment
- Consider SUD screening in patient's family to prevent diversion
- Sustained release preparations may reduce the risk of chemical dependency
- Abide by school medication administration protocols

Pediatrics. 2019;144(4):e20192528.

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Nonstimulants – Overview

Medication	Mechanism of Action	Side Effects	Considerations
Atomoxetine	SNRI – selectively inhibits reuptake of norepinephrine	Tachycardia, hypertension, initial somnolence, GI symptoms, growth delays, hepatotoxicity **Boxed warning**: suicidal ideation in children & adolescents	Option for patients with tics or Tourette syndrome, or if stimulant diversion or misuse is a concern
Viloxazine		Tachycardia, hypertension **Boxed warning**: suicidal thinking & behavior	
Guanfacine	Alpha-2 agonist – theorized to improve delay-related firing of prefrontal cortex neurons	Somnolence, dry mouth, dizziness, irritability, headache, bradycardia, hypotension, and abdominal pain Guanfacine has a longer half-life & fewer side effects than clonidine	Taper off rather than abrupt discontinuation due to withdrawal syndrome/rebound hypertension Option for patients with tics or Tourette syndrome, or if stimulant diversion or misuse is a concern
Clonidine			

Strattera. Package insert. Lilly USA LLC; 2020.
Intuniv. Package insert. Shire US Inc; 2013.
Qelbree. Package insert. Catalent Pharma Solutions; 2021.
Kapvay. Package insert. Concordia Pharmaceuticals Inc; 2014.

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Nonstimulants – Counseling/Clinical Pearls

- While stimulants are first line treatment, certain patient specific factors can make nonstimulants the better option
- When choosing an alpha-adrenergic agonist, guanfacine may be preferred over clonidine because it is less sedating and can be given in fewer daily doses
- **Guanfacine ER** and **clonidine ER** are FDA-approved both as monotherapy and as an adjunctive therapy to stimulants

Pediatrics. 2019;144(4):e20192528.

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ADHD Medication Contraindications

Medication	Contraindications
Amphetamines Methylphenidates	Symptomatic cardiovascular disease, moderate to severe hypertension, hyperthyroidism, hypersensitivity or idiosyncrasy to sympathomimetic amines, motor tics or Tourette syndrome, glaucoma, agitated states, anxiety, history of substance use disorder, concurrent use or use within 14 days of the administration of MAOIs
Atomoxetine	Hypersensitivity, concurrent use or use within 14 days of the administration of MAOIs, glaucoma, current or history of pheochromocytoma, severe cardiovascular disorders
Viloxazine	Concomitant use with or within 14 days of MAOIs; concomitant use of sensitive CYP1A2 substrates or CYP1A2 substrates with a narrow therapeutic range
Clonidine (ER)	Hypersensitivity
Guanfacine (ER)	Hypersensitivity

Strattera. Package insert. Lilly USA LLC; 2020. Kapvay. Package insert. Concordia Pharmaceuticals Inc; 2014. Qelbree. Package insert. Catalent Pharma Solutions; 2021. Adderall. Package insert. Shire US Inc; 2013. Intuniv. Package insert. Shire US Inc; 2013. Concerta. Package insert. ALZA Corporation; 2007.

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Comorbid Conditions

- Co-occurring mental, behavioral, and developmental disorders (MBDDs)
  - MEBs (mental, emotional, behavioral)
    - Anxiety, depression, tic/Tourette syndrome, behavioral or conduct problems, ODD
  - DLLDs (developmental, learning, language disorders)
    - ASD, learning disabilities, language and speech disorders
- A study from 2022 found 77.9% of children aged 3–17 years with current ADHD had one or more concomitant MBDD; 63.6% had a co-occurring MEB and 46.3% had a co-occurring DLLD

J Clin Child Adolesc Psychol. 2024;53(3):343-360.

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Comorbid Condition Considerations

Tic/Tourette disorders	Although alpha adrenergic agonists are only modestly effective against tics, they are used by some pediatric psychiatrists as first-line therapy in patients with early or mild tics
Misuse/diversion concern	Nonstimulants have a lower abuse potential than stimulants
Bipolar disorder	Monotherapy with second generation antipsychotics may help with ADHD symptoms, but if not effective, a stimulant can be added on
Depression	In adolescents, symptoms of inattention can be part of depression, therefore establishing a timeline for when symptoms of inattention developed will help guide treatment
Anxiety	Stimulants can increase symptoms of anxiety

J Clin Child Adolesc Psychol. 2024;53(3):343-360.

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Treatment Plan for Under 6 Years

- AAP recommends behavioral interventions prior to trying medication
- PTBM involves teaching parents age-appropriate developmental expectations, behaviors that strengthen the parent-child relationship, and specific management skills for problem behaviors
- If improvement is not seen from behavioral interventions after 8 – 12 weeks and decision to start medication is made, recommend methylphenidate
- Follow up for monitoring of side effects and titrate up dose until therapeutic effect observed

Pediatrics. 2019;144(4):e20192528.

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Treatment Plan for 6 Years and Older

- AAP recommends combining medication treatment with behavioral therapy
- Stimulants are first line and effective in up to 90% of patients
- Long-acting formulations are recommended
- Treatment will depend on patient and family preferences and comorbidities
- Follow up for monitoring of side effects and up titrate dose until therapeutic effect observed

J Clin Child Adolesc Psychol. 2024;53(3):343-360.

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Long-Acting Stimulant Medications for Treatment of ADHD

	Methylphenidate-Based Medications	Amphetamine-Based Medications
Liquids	• Quillivant® XR (Brand only; Methylphenidate HCl ER oral suspension) • Aptensio® (Brand only; Methylphenidate and dexmethylphenidate oral capsules)	• Dyanavel® XR (Brand only; Amphetamine ER oral suspension) • Adzenys® ER (Brand only; Amphetamine ER oral suspension) • Vyvanse™ (Generic; Lisdexamfetamine dimesylate capsules)
	Advantages: easy to swallow, easy to make small dose adjustments - especially when first starting treatment[1,2], different flavors **Disadvantages:** some patients may not like the flavor	
Chewable Tablets	• QuilliChew® ER (Brand only; Methylphenidate HCl ER chewable tablets)	• Dyanavel® XR (Brand only; Amphetamine ER chewable tablets) • Vyvanse™ (Generic; Lisdexamfetamine dimesylate chewable tablets)
	Advantages: different flavors **Disadvantages:** some patients may not like the flavor	
Oral Disintegrating Tablets	• Cotempla® XR-ODT (Brand only; Methylphenidate ER orally disintegrating tablet)	• Adzenys® XR-ODT (Brand only; Amphetamine ER orally disintegrating tablet)
	Advantages: dissolves quickly, no liquid is needed to take the tablet, does not need to be swallowed whole **Disadvantages:** some patients may not want to place medicine under their tongue	
Sprinkles	• Focalin® XR (Generic; Dexmethylphenidate HCl ER oral capsules) • Metadate® CD (Generic; Methylphenidate HCl ER (CD) oral capsules) • Ritalin® LA (Generic; Methylphenidate HCl ER (LA) oral capsules) • Aptensio® XR (Generic; Methylphenidate HCl ER (XR) oral capsules) • Jornay® PM (Brand only; Methylphenidate HCl ER oral capsules) • Azstarys® (Brand only; Serdexmethylphenidate and dexmethylphenidate oral capsules)	• Adderall® XR (Generic; Amphetamine-Dextroamphetamine capsules, or mixed amphetamine salts capsules) • Vyvanse™ (Generic; Lisdexamfetamine dimesylate capsules, or chewable tablets[3]) • Dexedrine® Spansule® (Generic; Dextroamphetamine sulfate ER oral capsules) • Mydayis™ (Brand only; mixed salts of a single-entity amphetamine ER capsules)
	Advantages: capsules can be opened and the medication "sprinkled" on food **Disadvantages:** some patients may have oral texture sensitivity to the small beads (Note: Azstarys and Vyvanse capsules contain powder, not beads)	
Transdermal Patches	• Daytrana® (Generic; Methylphenidate transdermal system)	• Xelstrym™ (Brand only; Dextroamphetamine transdermal system)
	Advantages: applied directly to skin, patch can be cut to optimize dose (off-label); patch can be kept on beyond 9 hours (off-label) **Disadvantages:** takes longer to start working, a mild or moderate temporary rash is not uncommon	
Crushables	• QuilliChew® ER (Brand only; Methylphenidate HCl ER chewable tablets)	• Dyanavel® XR (tablets) (Brand only; Dextroamphetamine transdermal system) • Vyvanse™ (Generic; Lisdexamfetamine dimesylate chewable tablets)
	Advantages: helpful for patients who cannot easily swallow pills; if the tablets are crushed, the medication may be "hidden" within food **Disadvantages:** not flavored, possibly bitter if not "hidden" within food	
Non-Chewable Tablets	• Concerta® (Generic; Methylphenidate HCl ER (ESM) tablets)	----------
	Advantages: ---------- **Disadvantages:** must be swallowed whole	

Short-Acting Stimulant Medications for Treatment of ADHD

	Methylphenidate-Based Medications	Amphetamine-Based Medications
Liquids	• Methylin® (Generic; Methylphenidate HCl oral solution)	• ProCentra® (Generic; Dextroamphetamine sulfate oral solution)
	Advantages: easy to swallow, easy to make small dose adjustments, especially when first starting treatment, different flavors **Disadvantages:** some children may not like the flavor	
Chewables	• Methylin® (Generic; Methylphenidate HCl chewable tablets); Brand name is no longer available	----------
	Advantages: different flavors **Disadvantages:** some patients may not like the flavor	
Oral Disintegrating Tablets	----------	• Evekeo® ODT (Brand only; Amphetamine sulfate oral disintegrating tablets)
	Disadvantages: dissolves quickly, no liquid is needed to take the tablet, does not need to be swallowed whole **Disadvantages:** some patients may not want to place medicine under their tongue	
Crushables	• Ritalin® (Generic; Methylphenidate HCl oral tablet)	• Adderall® (Amphetamine-Dextroamphetamine tablets, or Mixed amphetamine salts tablets)
	• Focalin® (Generic; Dexmethylphenidate HCl oral tablet)	• Zenzedi® (Dextroamphetamine sulfate tablet at the 5, 7.5, 15 and 20 mg doses. Brand only at the 2.5 and 7.5 mg doses)
	• Methylin® (Generic; Methylphenidate HCl chewable tablet); Brand name is no longer available	• Evekeo® (Brand only; Amphetamine sulfate tablets)
	Advantages: helpful for patients who cannot easily swallow pills; if the tablets are crushed, the medication may be "hidden" within food **Disadvantages:** not flavored, possibly bitter if not "hidden" within food	

Pediatrics. 2019;144(4):e20192528. ADHDMedicationGuide.com

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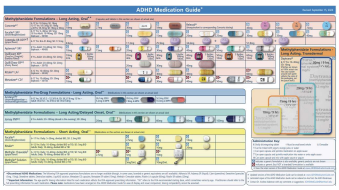

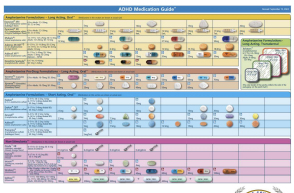

Pediatrics. 2019;144(4):e20192528. ADHDMedicationGuide.com

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Pt Case Example 1

KT is a 9-year-old female who is visiting her psychiatrist for a follow-up. She has been experiencing racing heart beats, irritability and trouble sleeping since starting Concerta® (18mg QAM) three weeks ago. Her mother, concerned about these side effects, would like the psychiatrist to switch her to an alternative treatment that is non-stimulating. Switching KT to which medication will address the mother's request?

a) Vyvanse®
b) Adderall XR®
c) Kapvay®
d) Daytrana®
e) Ritalin®

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Pt Case Example 1

KT is a 9-year-old female who is visiting her psychiatrist for a follow-up. She has been experiencing racing heart beats, irritability and trouble sleeping since starting Concerta® (18mg QAM) three weeks ago. Her mother, concerned about these side effects, would like the psychiatrist to switch her to an alternative treatment that is non-stimulating. Switching KT to which medication will address the mother's request?

a) Vyvanse®
b) Adderall XR®
c) **Kapvay® -** Clonidine is a nonstimulant and is not associated with the insomnia & irritability that stimulants may cause
d) Daytrana®
e) Ritalin®

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Pt Case Example 2

TM is a 7-year-old male who has just gotten diagnosed with Tourette syndrome. He has been on Adderall® for 2 months to treat his ADHD. His parents have noticed little benefit regarding his ADHD symptoms and that TM has been more irritable recently. TM's psychiatrist would like to switch him to an alternative treatment that will be effective to treat both his TS and ADHD. Switching TM to which medication may provide benefit regarding both of TM's diagnosis?

a) Ritalin®
b) Intuniv®
c) Vyvanse®
d) Daytrana®

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Pt Case Example 2

TM is a 7-year-old male who has just gotten diagnosed with Tourette syndrome. He has been on Adderall® for 2 months to treat his ADHD. His parents have noticed little benefit regarding his ADHD symptoms and that TM has been more irritable recently. TM's psychiatrist would like to switch him to an alternative treatment that will be effective to treat both his TS and ADHD. Switching TM to which medication may provide benefit regarding both of TM's diagnosis?

a) Ritalin®
b) Intuniv® - alpha-2-adrenergic agonists are associated with improvements in ADHD symptoms and comorbid tics
c) Vyvanse®
d) Daytrana®

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Part 2 – ADHD Treatment Barriers, Medication Shortages And Alternative Therapies

Presented By: David Gamez, Pharm.D

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Objectives

Discuss medication shortages
- Supply & demand, role of manufacturer, DEA quotas, and solutions

Explore therapeutic alternatives as workaround to shortages
- Novel, upcoming, and existing treatments options

Review structural and attitudinal barriers to ADHD treatment
- Premature discontinuation of therapy
- Racial and ethnic disparities
- Transitions of care from pediatric to adult

18 Years Featuring South Florida Pharmacy Residents

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Key Challenges

Medication Shortages	Suboptimal Long-Term Outcomes	High Rates of Treatment Discontinuation
• Telemedicine increasing health care accessibility • Increasing demand • Manufacturers fail to keep pace	• 60% of children with ADHD continue to experience symptoms into adulthood • Impacts employment opportunities and relationships	• 50% of adolescents discontinue therapy within 2 years • Side effects, lack of perceived benefit, and/or stigmas

American Psychiatric Association, 2020. *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)*.
Bridell, S. Yea, H. Li, L. Astrup, A. Gao, L. Gillies, M. (2023

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Limited Access to Medications

Challenges
- Limited availability of ADHD medications
  - Controlled substance quotas, manufacturing delays, regulatory changes
- High out-of-pocket costs

Impact
- Reduced treatment adherence
- Disparities in access for marginalized communities
  - Racial and ethnic minorities less likely to seek and receive treatment

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ADHD Medication Shortages

Scope of the Problem:

Increased demand: largest single-year annual change in new stimulant prescriptions exceeding 10% in most age groups (2021-2022)

Manufacturing delays and DEA production quotas

Supply chain disruptions exacerbated by the COVID-19 pandemic

Impact on Patients:

Treatment interruptions leading to symptom relapse

Increased stress for families and caregivers

Hagebloh GM. Supply Chains and the COVID-19 Pandemic: A Comprehensive Framework. European Management Review. 2021 Autumn;18(3):263-82. doi: 10.1111/emre.12469. Epub 2021 Feb 8. PMCID: PMC8014293.

FDA, 2022. *Drug Shortages: Impact of ADHD Medication Shortages.*

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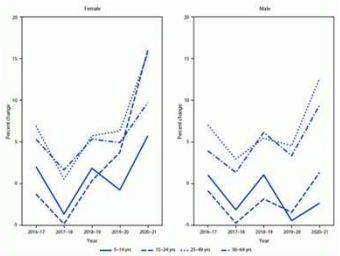
ADHD Medication Shortages

Figure 1. Relative annual percent change in percentage of persons aged 5-64 years with at least one stimulant prescription fill, by sex and age group – MarketScan commercial databases, United States, 2016-2021



Danielson ML, Bohm MK, Newsome K, et al. Trends in Stimulant Prescription Fills Among Commercially Insured Children and Adults — United States, 2016–2021. MMWR Morb Mortal Wkly Rep 2023;72:337–342. DOI: http://dx.doi.org/10.15585/mmwr.mm7213a1

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ADHD Medication Shortages

2023: DEA publishes letter to American public

- Acknowledged shortage of stimulant medications
- Noted manufacturers were NOT producing full amount based on quota
  - Occurred in consecutive years ('22-'23)
- DEA changes quota allocation process

U.S. Department of Justice
Drug Enforcement Administration

November 1, 2023

Dear Americans:

(US DOJ: DEA, Nov. 1st 2023)

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Addressing Shortages: Alternate Pharmacological Options

Stimulant Substitutes	• Switch between amphetamine- and methylphenidate-based medications (e.g., Adderall® to Ritalin®)
Non-Stimulant Options	• Atomoxetine (Strattera®) • Guanfacine (Intuniv®) and Clonidine (Kapvay®)
Off-Label Alternatives	• Bupropion (Wellbutrin®) • Modafinil (Provigil®)
Considerations	• Monitor efficacy and side effects • Tailor choices to patient-specific needs

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Alternate Pharmacological Options

Atomoxetine vs. placebo in children and adults with ADHD (Durell et al., 2013)

- Atomoxetine demonstrated a 45% reduction in ADHD symptoms (measured using the ADHD-Rating Scale IV [ARS-IV]), compared to a 10% reduction in the placebo group (p-value = 0.001)
  - Effective for ADHD patients with comorbid anxiety or depression
  - Significant improvements in social and emotional functioning, with an effect size of 0.6 vs. 0.2 for placebo
- Comparable efficacy to stimulant medications in controlling ADHD symptoms in non-responders to stimulants (Biederman et al., 2004)

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Alternate Pharmacological Options

Guanfacine vs. placebo in children with ADHD (Sallee et al., 2009)

- Guanfacine led to a 40% reduction in ADHD symptoms (measured using ARS-IV), compared to a 5% reduction with placebo (p-value = 0.002)
- Guanfacine showed similar efficacy to stimulant medications (methylphenidate) in improving hyperactivity and impulsivity in children who were non-responders to stimulants (Biederman et al., 2010)

Clonidine also showed a 35% improvement in symptoms, with a 30% improvement in impulsivity and hyperactivity (effect size = 0.5)

45

Alternate Pharmacological Options

A Systematic Review of the Use of Bupropion for Attention-Deficit/Hyperactivity Disorder in Children and Adolescents (Ng QX, 2016)

- 25,455 articles published since January 1, 1988 and May 1, 2016 on bupropion use in ADHD
  - Only 6 articles on clinical trials involving children
- Bupropion led to a 35% reduction in ADHD symptoms (measured by ARS-IV), compared to a 12% reduction in the placebo group (p-value = 0.03)
- 3 head-to-head trials found that bupropion had efficacy comparable to methylphenidate ($p > 0.05$)
  - Particularly in those with comorbid depression
  - Headache observed more frequently in methylphenidate group

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Alternate Pharmacological Options

Modafinil in children and adolescents with attention-deficit/hyperactivity disorder: a preliminary 8-week, open-label study (Boellner et. al., 2006)

- Improved symptoms on all ADHD rating scales and subscales
- Mean change in total score (measured by ARS-IV) was -14.6%, and a -7.6% and -6.9% in the inattention and hyperactivity-impulsivity scores, respectively
- Significant improvements in cognitive function and attention
- Modafinil's effects on attention and cognitive function were comparable to methylphenidate, with fewer side effects related to appetite suppression and sleep disruption.

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Practice Question #1

1. What are the most common short-term adverse effects of stimulants?
   a. Appetite loss
   b. Abdominal pain
   c. Headaches
   d. Sleep disturbances
   e. All of the above

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Practice Question #1

1. What are the most common short-term adverse effects of stimulants?
   a. Appetite loss
   b. Abdominal pain
   c. Headaches
   d. Sleep disturbances
   e. All of the above

49

The Future of ADHD Treatments

1. Neurostimulation Therapy: Transcranial Magnetic Stimulation (TMS)
2. Targeted Gene Therapy
3. Vortioxetine (Cognitive Enhancer and Antidepressant)
4. The Multimodal Treatment of ADHD

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Neurostimulation Therapy: Transcranial Magnetic Stimulation (TMS)

Non-invasive neuromodulation technique that modulates brain activity using targeted, non-invasive approach

- Electromagnetic coils generate electrical currents in underlying neural tissue

2019 meta-analysis found that TMS showed significant improvements in ADHD compared to placebo (Journal of Psychiatric Research)

- TMS was associated with a 30% reduction in ADHD symptoms (measured by [ARS-IV]) compared to a 5% reduction in the placebo group (p-value = 0.03)
- TMS group had significantly better outcomes in attention and executive functioning tasks (difference in means = 10.5 points vs. 2.2 points for placebo group)
- Outperformed placebo in reducing hyperactivity and impulsivity (effect size: 0.45)

Team N editorial. TMS Therapy for ADHD: A Comprehensive Guide to Transcranial Magnetic Stimulation Treatment. Neurolaunch.com. Published August 4, 2024. https://neurolaunch.com/tms-therapy-adhd/

51

Neurostimulation Therapy: Transcranial Magnetic Stimulation (TMS)

Potential Benefits

- Improve attentions and focus
- Reduce impulsivity
- Enhance executive function skills
- Decrease hyperactivity
- Improve working memory

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Genome Guided Personalized Drug Therapy

ADHD is a polygenic disorder with contributions from multiple genes

- Heritability of ADHD is 70-80%
- Commonly via single nucleotide polymorphisms (SNPs)
- Rare variants associated with neurometabolic syndromes

Key genetic alterations in ADHD

- Variants in dopamine-related genes
  - DRD4: receptor sensitivity, DAT1 (SLC6A3): transporter activity
- Variants in norepinephrine-related genes
  - ADRA2A: receptor function
- Variants in serotonin-related genes
  - 5-HTTLPR: transporter regulation

Hawki J. Genome Guided Personalized Drug Therapy in Attention Deficit Hyperactivity Disorder. Front Psychiatry. 2022 Jun 27;13:925442. doi: 10.3389/fpsyt.2022.925442. PMID: 35832601; PMCID: PMC9271625.

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Genome Guided Personalized Drug Therapy

Genomic Analysis

- Whole exome/genome sequencing

Implementation

- Start with patients having rare, high-impact genetic alterations
- Expand to include broader ADHD populations with common genetic SNPs
- Develop targeted therapies based on biomarker and genetic screening

Hawki J. Genome Guided Personalized Drug Therapy in Attention Deficit Hyperactivity Disorder. Front Psychiatry. 2022 Jun 27;13:925442. doi: 10.3389/fpsyt.2022.925442. PMID: 35832601; PMCID: PMC9271625.

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Genome Guided Personalized Drug Therapy

Benefits

- Precise and tailored drug therapy based on SNPs
- Reduced side effects
  - Avoiding medications contraindicated by genetic profile
- Improved efficacy by targeting specific dopamine, serotonin or norepinephrine pathways

Limitations

- High cost
- Limited understanding of ADHD genetic heterogeneity

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Trintellix (Vortioxetine)

MOA: Serotonin modulator and stimulator

- Direct serotonin modulation enhances antidepressant effects and potentially influences cognitive function

Vortioxetine demonstrated a 22% reduction in ADHD symptoms, compared to a 5% reduction with placebo (p-value = 0.02)

- Significant improvement in executive functioning and attention, with a 15-point improvement on the Stroop Test of Cognitive Control vs. 3 points for placebo
- Demonstrated a 2.3-fold greater effect on task-switching performance and cognitive flexibility than placebo (p-value = 0.03)

Team N editorial. Trintellix for ADHD: An In-Depth Exploration of Its Potential Benefits and Limitations. Neurolaunch.com. Published August 4, 2024. Accessed January 13, 2025. https://neurolaunch.com/trintellix-for-adhd/

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Multimodal Treatment Approaches

What is Multimodal Treatment?

- Combines medication, behavioral therapy, psychoeducation, and lifestyle interventions to address diverse needs of individuals with ADHD

Evidence from the Multimodal Treatment of ADHD (MTA) Study

- Combination of medication + behavioral therapy showed superior outcomes to medication and CBT alone
- Improved academic, social, and emotional functioning

Benefits

- Addresses both core symptoms and associated challenges
- Adapts to the fluctuating nature of ADHD

MTA Cooperative Group, 1999. *A 14-month randomized clinical trial of treatment strategies for attention-deficit hyperactivity disorder.*

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The MTA Study

Examined the long-term course of ADD/ADHD from childhood into adulthood, focusing on the fluctuating nature of the disorder

Participants

- Nearly 600 children, aged 7-9, diagnosed with ADHD

Treatment Groups (randomly assigned)

1. Intensive medication management alone
2. Intensive behavioral treatment alone
3. A combination of both medication and behavioral treatments
4. Routine community care (control group)

MTA Cooperative Group, 1999. *A 14-month randomized clinical trial of treatment strategies for attention-deficit hyperactivity disorder.*

18 Years Fostering

South Florida Pharmacy Residency

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The MTA Study: Key Findings

Fluctuating Course

- 63.8% of participants experienced a fluctuating course of ADHD characterized by alternating periods of remission and recurrence over 16 years

Multiple Fluctuations

- On average, individuals in the fluctuating subgroup experienced about 3.58 periods of remission and recurrence, indicating significant variability in symptom expression over time

Predictors of Fluctuation

- Childhood factors such as symptom severity, comorbid conditions, and environmental influences

Implications for Treatment

- ADHD is a dynamic condition with periods of improvement and recurrence

MTA Cooperative Group, 1999. *A 14-month randomized clinical trial of treatment strategies for attention-deficit hyperactivity disorder.*

18 Years Fostering

South Florida Pharmacy Residency

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The MTA Study

Effectiveness of Treatments

- Medications alone and combination treatment were more effective than behavioral therapy and placebo alone
- Combination treatment offered additional benefits in areas such as oppositional behaviors, internalizing symptoms, and parent-child relations

Long-Term Outcomes (follow-up studies)

- Initial superiority of medication management diminished over time
- Sustained improvement was associated with the quality and consistency of treatment

Implications

- Highlights importance of personalized treatment approaches for children with ADHD
- Medications can be highly effective in the short term
- Combining medications with behavioral interventions may offer broader and more sustained benefits.

MTA Cooperative Group, 1999. *A 14-month randomized clinical trial of treatment strategies for attention-deficit hyperactivity disorder.*

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Benefits of MTA Interventions

Comprehensive Care
- Integrates multiple treatment modalities

Enhanced Outcomes
- Combining treatments can lead to improved symptom management, better functional outcomes, and enhanced quality of life for individuals with ADHD

Personalized Treatment
- Tailoring the combination of therapies to the individual's specific needs ensures a more effective and comprehensive management plan

Long-Term Benefits
- Sustained multimodal treatment may contribute to long-term improvements in academic performance, social interactions, and overall well-being

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Barriers to MTA Adoption

Limited Availability of Behavioral Therapists
- A shortage of trained clinicians, particularly in rural areas, limits the accessibility of behavioral therapy

Insurance Constraints
- Many insurance plans prioritize medications over behavioral therapy or have high co-pays for therapy sessions, making multimodal care less accessible

Parental Education
- Parents may not be fully informed about the benefits of multimodal treatments and may not understand how therapy and medication can complement each other

(Hilty et al., 2017).

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Benefits of Novel ADHD Treatments

- The potential of more precise treatments targeting the neurological, cognitive, and emotional aspects of ADHD
- Fewer incidence of side effects compared to traditional stimulants
- Long-term studies will be necessary to confirm the durability of these treatment effects and their safety profiles

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Question #2

2. Of the listed agents, which is a FDA approved alternative to 1st line stimulant medications during periods of drug shortages?

a. Guaifenesin
b. Vortioxetine
c. Guanfacine
d. All of the above

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Question #2

2. Of the listed agents, which is a FDA approved alternative to 1st line stimulant medications during periods of drug shortages?

a. Guaifenesin (Robitussin®)
b. Vortioxetine (Trintellix®)
c. Guanfacine (Intuniv®)
d. All of the above

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Barriers To Care

Structural Barriers:

- Limited access to specialized healthcare providers in underserved and rural areas
- High costs of medications and treatment
- Lack of integration between educational, medical, and psychological services

Attitudinal Barriers:

- Stigma surrounding ADHD diagnosis and treatment
  - Reluctance to seek care or accepting diagnosis
- Misconceptions about ADHD being a "behavioral issue" rather than disease state requiring treatment

Premature Discontinuation:

- 50% of adolescents discontinue therapy < 2 years due to side effects, stigma, or perceived inefficacy

Bitsko, I. Yoo, H, Li, L, Astrup, A. Gao, L. Gillies, M. (2023).
Centers for Disease Control and Prevention (CDC), 2021

66

Stigma and Attitudinal Barriers

Sources of Stigma	• Negative perceptions of ADHD • Parental reluctance due to societal judgment
Impact on Treatment	• Delayed diagnosis • Lower treatment initiation rates
Supporting Evidence	• Parental beliefs and lack of understanding identified as major barriers (SAGE Open Medicine)

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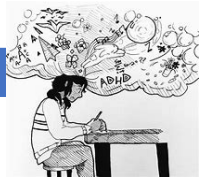
Limited Understanding and Awareness

Key Issues

- Parents and providers often lack awareness of ADHD symptoms
- Misconceptions delay treatment



Solutions

- Educational campaigns
- Training for healthcare providers

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Healthcare System Limitations

Barriers

- Long wait times
- Limited mental health resources

Impact

- Delayed diagnosis and treatment
- Self-diagnosis and complications

Supporting Evidence

- Extended wait periods harm outcomes (The Times)

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Premature Discontinuation of Therapy

By the Numbers	• 47% of adolescents discontinue ADHD medication within one year
Reasons	• Side effects • Perceived ineffectiveness • No/lost insurance coverage
Impact	• Poor long-term health and academic outcomes
Solution	• Monitoring and adjusting medication regimens to minimize side effects and improving communication between healthcare providers and families.

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Racial and Ethnic Disparities

Challenges
- Lower diagnosis and treatment rates in minority groups
- Biases in healthcare

Impact
- Widening health inequities

Supporting Evidence
- Structural and cultural differences highlighted (Psychiatric Services)

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Strategies to Mitigate Medication Shortages

Policy Advocacy	Improved Supply Chain	Patient-Centric Approaches
• Increase DEA quotas for stimulant production • Expedite FDA approvals for proven alternative medications	• Strengthen global pharmaceutical logistics • Diversify manufacturing sources • Utilizing digital tools like AI to predict demand surges	• Educate patients about potential alternatives • Foster open communication between patients and providers

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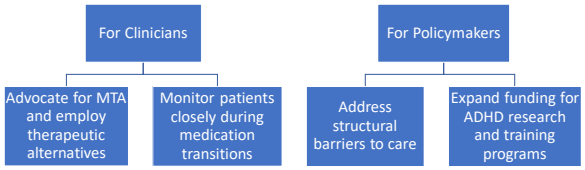
Recommendations for Clinicians and Policymakers



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Addressing These Needs Matters

Reducing barriers to care

- Ensures timely diagnosis and access to appropriate care by trained specialist

Solutions to address medication shortages

- Shortages cause treatment delays and exacerbate symptoms
- Understanding alternative treatments can help ensure continuity of care

Using multimodal treatment approaches for improved and sustained long-term outcomes

- Addresses both core ADHD symptoms and related challenges, leading to better academic, social, and emotional outcomes

Call to action

- Collaboration among clinicians, policymakers, educators, and families is crucial to ensuring equitable, effective, and continuous ADHD care
- Encourage advocacy efforts to improve access and reduce the stigma surrounding ADHD

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Challenges in Pediatric Population Management of ADHD

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January 26, 2025

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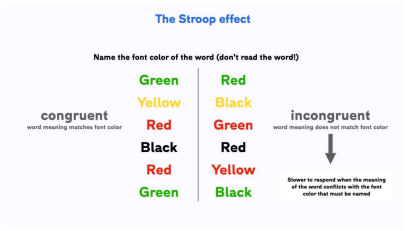

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Rising Concerns with Under Vaccinated Children

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January 26, 2025

1

Financial Disclosures

No one in control of the content of this activity has a relevant financial relationship with an ineligible company as defined by the Standards of Integrity and Independence in Accredited Continuing Education definition of an ineligible company.

2

Learning Objectives

- Analyze the epidemiological trends of childhood vaccination rates in the U.S.
- Outline the consequences of low vaccination rates on public health and the education system
- Consider potential reasons for declining childhood vaccination rates in the U.S.
- Discuss regulations governing vaccine exemptions for children in Florida
- Examine ways in which pharmacists can positively impact public perception of childhood vaccines

3

Abbreviations

- **CBER:** Center for Biologics Evaluation and Research
- **CDC:** Centers for Disease Control and Prevention
- **DTaP:** Diphtheria, Tetanus, and Acellular Pertussis
- **Hib:** Haemophilus Influenzae type B
- **HPV:** Human Papillomavirus
- **MMR:** Measles, Mumps, and Rubella
- **mRNA:** Messenger Ribonucleic Acid
- **RSV:** Respiratory Syncytial Virus
- **SHOTS:** State Health Online Tracking System
- **TDaP:** Tetanus, Diphtheria, and Acellular Pertussis
- **VAERS:** Vaccine Adverse Events Reporting System

4

Definitions

Outbreak: An increase in the incidence of a disease state above the level of what would normally be expected in a certain geographic area; often sudden in nature

Epidemic: Same definition as an outbreak, but is often used colloquially to refer to outbreaks which occur on a larger geographic scale

Pandemic: An epidemic that has spread across countries or continents, usually affecting large numbers of people

Centers for Disease Control and Prevention. Reproductive Health Glossary. (2021)

5

Recommended Vaccines in Childhood

Birth to 15 months of age:

- RSV
- Hepatitis B
- Rotavirus
- DTaP
- Hib
- Pneumococcal
- Inactivated poliovirus
- COVID-19
- Influenza
- MMR
- Varicella
- Hepatitis A

Centers for Disease Control and Prevention. Child and Adolescent Immunization Schedule. (2023)

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Recommended Vaccines in Childhood

18 months to 18 years of age:

- Hepatitis B
- DTaP
- Inactivated poliovirus
- COVID-19
- Influenza
- MMR
- Varicella
- Hepatitis A
- TDaP
- HPV
- Meningococcal

Centers for Disease Control and Prevention. Child and Adolescent Immunization Schedule. (2023)

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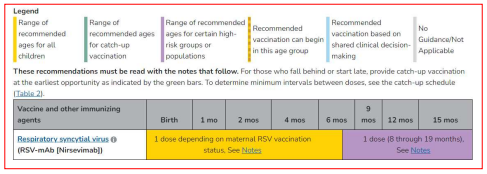
2025 ACIP-Approved Immunization Schedules

- Link to child and adult immunization schedules:
  - https://www.cdc.gov/vaccines/hcp/imz-schedules/index.html



Centers for Disease Control and Prevention. Child and Adolescent Immunization Schedule. (2023)

8

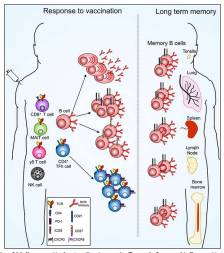
Types of Vaccines

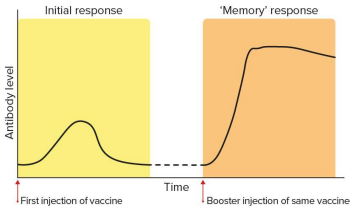
- **Live-attenuated**
  - MMR, Varicella
- **Inactivated**
  - Polio, Hepatitis A
- **Recombinant**
  - HPV, Hib
- **mRNA**
  - Pfizer/Moderna COVID-19
- **Toxoid**
  - DTaP
- **Viral Vector**
  - Johnson & Johnson COVID-19

U.S. Department of Health and Human Services. Types of Vaccines. (2021)

9

Immunology





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10

Maternal Antibodies

13 weeks' gestation: antibodies from mother's immune system begin to cross the placenta

2-3 months of age: infant immune system matures

6-12 months of age: maternal immunity wanes

Front Immunol. 2014 Sep 16;5:446.

11

Childhood Vaccination: Trends and Epidemiology

12

Childhood Vaccinations: Epidemiology

- From the 2019-2020 school year to the 2023-2024 school year, national vaccination coverage for kindergarten-aged children declined from 95% to 92.7%
- In the past year, the vaccine exemption rate for kindergarteners increased from 3% to 3.3%

What is the significance?

- This represents a departure from a 10-year trend of having a ~95% vaccination rate among kindergarteners
- Herd immunity for certain diseases can be significantly impacted if vaccination rates fall below a given threshold (ex: measles)

MMWR Morb Mortal Wkly Rep 2019;68:905–912.
MMWR Morb Mortal Wkly Rep 2024;73:925–932.

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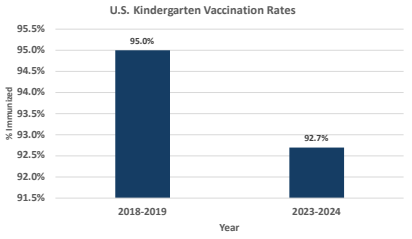
Childhood Vaccinations: Epidemiology



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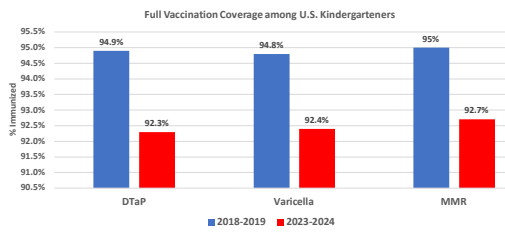
Childhood Vaccinations: Epidemiology



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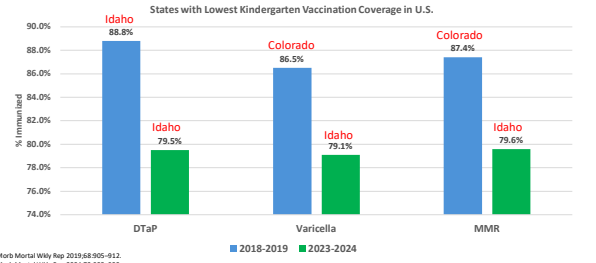
Childhood Vaccinations: Epidemiology



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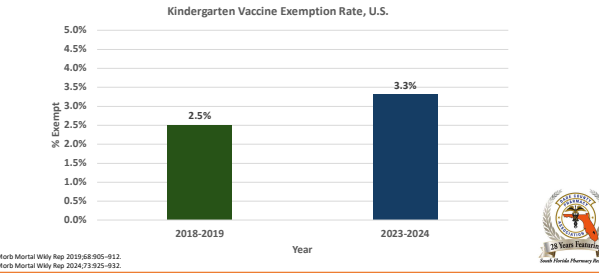
Childhood Vaccinations: Epidemiology



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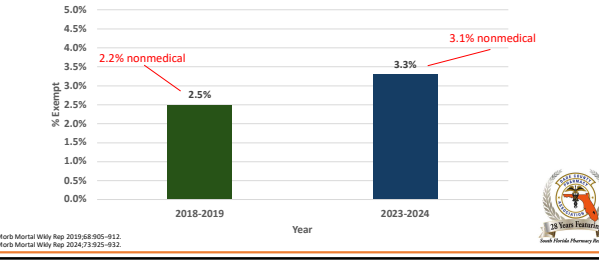
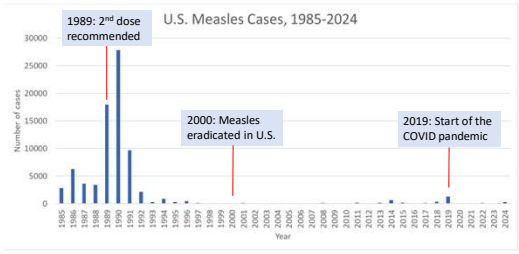
Childhood Vaccinations: Epidemiology



MMWR Morb Mortal Wkly Rep 2019;68:905–912.
MMWR Morb Mortal Wkly Rep 2024;73:925–932.

18

Measles Outbreaks



Centers for Disease Control and Prevention. Measles Data and Research. (2023)

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Consequences of Low Vaccination Rates in Children

20

Consequences of Declining Childhood Vaccination Rates

Negative implications of low vaccination rates extend beyond the individual

- Decreased societal resistance to future outbreaks
- Absenteeism from school and work
- Increased hospitalizations and healthcare costs associated with the treatment of preventable diseases
- Decreased protection for children and adults with medical exemptions to vaccination
- Proliferation of antimicrobial resistance

National Foundation for Infectious Diseases. The Implications of Low Vaccination Rates. (2022)

21

Community Protection and Decreased Resistance to Outbreaks

Community protection: indirect reduction in disease transmission achieved through vaccination, also known as "herd immunity"

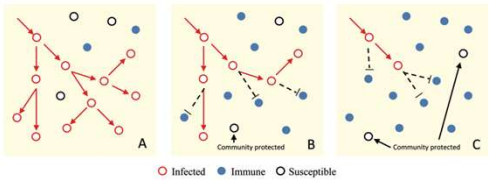
Limitations:

- Applies to diseases which require human reservoirs
- Not all vaccines have the same effect at reducing disease transmission
- Selection pressures may cause non-vaccine serotypes of infection to circulate with greater frequency

Clin Infect Dis. 2018 Jul 18;67(3):464-471.

22

Community Protection and Decreased Resistance to Outbreaks



Clin Infect Dis. 2018 Jul 18;67(3):464-471.

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Community Protection and Decreased Resistance to Outbreaks

Infectious Pathogen	Threshold for Community Protection (%)
Diphtheria	83-85
Influenza	30-75
Measles	92-94
Mumps	75-86
Pertussis	80-94
Polio	50-95
Rubella	83-85
Smallpox	80-85

Clin Infect Dis. 2018 Jul 18;67(3):464-471.

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Community Protection and Decreased Resistance to Outbreaks

Populations who may not be eligible to get vaccinated:

- Age
- Comorbid conditions
- Chemotherapy
- Vaccine failure
- Primary or acquired immunodeficiencies

Clin Infect Dis. 2018 Jul 18;67(3):464-471.

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Absenteeism as a Result of Undervaccination

Chronic Absenteeism

- Defined as missing >10% of school days during a given school year
- While numerous factors can contribute to chronic absenteeism, the U.S. Department of Education has identified vaccine-preventable illness as a significant contributor

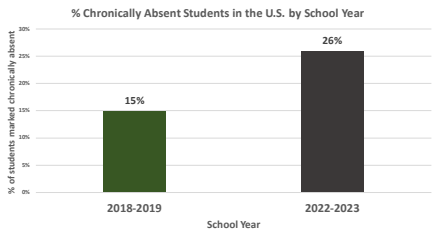
Rate of chronic absenteeism among public school students in Florida

- 2018-2019: **20%**
- 2022-2023: **30.9%**

U.S. Department of Education. Chronic Absenteeism. (2023)

26

Chronic Absenteeism Before and After the COVID-19 Pandemic



U.S. Department of Education. Chronic Absenteeism. (2023)

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Impact of Chronic Absences on Individual and Societal Outcomes

Chronic absence from school has been shown to be associated with the following:

- Negative educational outcomes
- Negative social outcomes, such as increased rates of anxiety and depression
- Association with negative outcomes persists long after graduation

Invent Foundation. Addressing Chronic Absenteeism. (2024)

28

Healthcare Costs Associated with Vaccine-Preventable Illnesses

- Estimated that among children born from 1994-2023, routine childhood vaccinations will **prevent 32 million hospitalizations**, and result in direct and indirect savings rising above **$3 trillion** total
  - Also estimated to prevent over **1.1 million deaths**
- CDC estimates that for every $1 spent on childhood vaccination, the U.S. saves ~$11
- Annual economic burden of pertussis, influenza, herpes zoster, and pneumococcal infections: **$26.5 billion**
  - Not accounting for mortality cost

MMWR Morb Mortal Wkly Rep. 2023;73(31):771-773.

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U.S. Healthcare Costs Associated with Vaccine-Preventable Illnesses

Disease	Metric	Cost
Measles Outbreak	Average Cost per State	$140,000
Measles Outbreak	Total Cost, 2017 Hennepin County Outbreak	$1.3 million
HPV	Estimated Annual Cost (U.S)	$333 million
Pneumococcal Disease	Estimated Annual Cost (U.S.)	$1.86 billion
Influenza	Average Cost each Flu Season (U.S.)	$11.2 billion

Health Aff. 2017;36(3):476-484.

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Consequences of Declining Childhood Vaccination Rates

Negative implications of low vaccination rates extend beyond the individual

- Decreased societal resistance to future outbreaks
- Absenteeism from school and work
- Increased hospitalizations and healthcare costs associated with the treatment of preventable diseases
- Decreased protection for children and adults with medical exemptions to vaccination
- **Proliferation of antimicrobial resistance**

31

Question #1

Nationwide, the majority of kindergarten exemptions from immunization are for non-medical reasons.

a) True

b) False

32

Question #1

Nationwide, the majority of kindergarten exemptions from immunization are for non-medical reasons.

a) True

b) False

33

Causes of Declining Childhood Vaccination Rates in the Modern Era

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Vaccine Myths from the Past

Vaccines cause autism

- Lancet study from Wakefield, et al. published in 1998
- Has since been broadly debunked through multiple studies
- Retracted by the Lancet in 2010

Giving a child too many vaccinations at once is unsafe

- When new vaccines are licensed, they are tested along with all other vaccines that are already recommended
- While some combinations of vaccines can cause fevers, there is no evidence that giving multiple vaccinations at once causes negative long-term consequences

Eur J Paediatr Neurol. 2022; 36:151-158.

35

Vaccine Myths from the Past

Thimerosal

- Preservative traditionally found in vaccines
- Contains ethylmercury
- Proven to be safe at doses present in vaccines
- All routine vaccinations for children ages 6 and under are available without thimerosal

Aluminum

- Aluminum is used as an adjuvant in some childhood vaccines
- Quantities of aluminum present in vaccines is very low, and infants generally receive more aluminum from dietary sources in the first 6 months of life than from vaccines
- Aluminum content in vaccines is heavily monitored by the Center for Biologics Evaluation and Research (CBER)

Clin Chim Acta. 2015 Apr 15;444:212-20.

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Vaccine Hesitancy in the Current Era

Pre- vs. post-COVID era

- Operation Warp Speed
- Politicization of mRNA vaccines in the media

Declining vaccination rates among school-aged children across the country

- February 2024: measles outbreak in Weston, Florida
- 16 other measles outbreaks reported by the CDC in 2024 alone
  - 42% of cases in patients <5 years of age
  - 31% of cases in patients 5-19 years of age
  - 89% of cases occurred in unvaccinated patients

Centers for Disease Control and Prevention. Measles Data and Research. (2023)

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Vaccine Hesitancy in the Current Era

COVID-19 vaccine myths

- Natural immunity is safer and preferable to getting the vaccine
- The vaccine alters DNA
- Concerns regarding VAERS data
- Unsafe ingredients

Myths & Facts about Covid-19 Vaccines. Centers for Disease Control and Prevention. (2024)

38

Trust in Hospitals and Physicians: Pre-COVID vs. Post-COVID

- 50 state survey of U.S. adults 18+ years of age spanning from April 2020 to January 2024
- Surveys were distributed online in waves, approximately every 1 to 2 months throughout the study timeframe
- Incentivized survey
- Demographic quotas were implemented to target equal representation among participants studied

JAMA Netw Open. 2024 Jul 1;7(7):e2424984.

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Trust in Hospitals and Physicians: Pre-COVID vs. Post-COVID

Participant Demographics (n= 443,455)	
Mean age (years)	43.3
Female sex (%)	65
Race (%)	White- (71.1) Black- (11.1) Asian American- (5) Pacific Islander- (1.3) Native American- (0.7)

JAMA Netw Open. 2024 Jul 1;7(7):e2424984.

40

Trust in Hospitals and Physicians: Pre-COVID vs. Post-COVID

Results:

Question	% reporting "a lot" of trust	
	April 2020	January 2024
How much do you trust hospitals/physicians to do the right thing to handle the current coronavirus (COVID-19) outbreak?	71.5%	40.1%

- Higher levels of trust were associated with a greater likelihood of being vaccinated
- Predictors for decreased levels of trust included female sex, lower education level, lower income, and rural address

JAMA Netw Open. 2024 Jul 1;7(7):e2424984.

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Reasons for Lack of Trust in Health Institutions Post-COVID

- Online and telephone survey conducted in February 2022 among U.S. adults ages 18 and older
- 4,208 participants included
- Trust was measured on a Likert scale

Health Aff (Millwood). 2023 Mar;42(3):328-337.

42

Reasons for Lack of Trust in Health Institutions Post-COVID

Reason for Lack of Trust in Institution	CDC (n= 803)	State Health Dept. (n= 915)	Local Health Dept. (n=898)
Political influence on recommendations and policies	74%	72%	70%
Have given too many conflicting recommendations	73%	61%	58%
Private-sector influence on recommendations and policies	60%	53%	48%
Inconsistency in following scientifically valid research	51%	48%	43%
Restrictive recommendations go too far	44%	38%	42%
I don't trust the government generally	39%	39%	42%
Lack of action to stop the spread of COVID-19	35%	34%	31%

Health Aff (Millwood). 2023 Mar;42(3):328-337.

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Reasons for Lack of Trust in Health Institutions Post-COVID

Reason for Lack of Trust in Institution	CDC (n= 803)	State Health Dept. (n= 915)	Local Health Dept. (n=898)
Religious beliefs not respected	28%	25%	23%
Lack of fair treatment for rural communities	21%	21%	22%
Lack of fair treatment for racial and ethnic minority communities	19%	25%	20%

Health Aff (Millwood). 2023 Mar;42(3):328-337.

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Vaccine Exemptions: Florida Law

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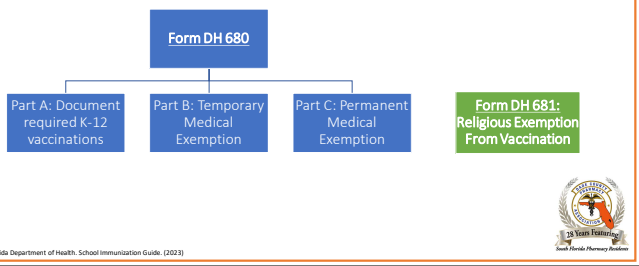
Vaccine Documentation



Florida Department of Health. School Immunization Guide. (2023)

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Types of Exemptions from Vaccination

Temporary Medical Exemption (Form DH 680)

- For those in the process of completing required immunizations; has an expiration date by which immunizations must be completed

Permanent Medical Exemption (Form DH 680)

- For use if a child cannot be fully immunized due to medical reasons; requires written documentation from physician stating reasons for exemption based on clinical judgement

Religious Exemption from Immunization (Form DH 681)

- Issued if immunizations are in conflict with religious beliefs of the guardian or parent

Florida Department of Health. School Immunization Guide. (2023)

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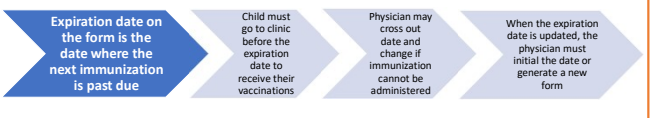
Temporary Medical Exemption (DH Form 680 Part B)



Florida Department of Health. School Immunization Guide. (2023)

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Temporary Medical Exemption (DH Form 680 Part B)

Exceptions to having a specific expiration date include:

- Physician accidentally signs Part A of the form instead of Part B
- For attendance at preschools located on a school campus, non-specific timeframes may be documented instead of a specific expiration date
- For attendance at childcare or family daycare, non-specific timeframes may be documented instead of a specific expiration date
- If it is determined that a vaccine shortage exists, extended expiration dates may be granted by the Department of Health

Florida Department of Health. School Immunization Guide. (2023)

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Permanent Medical Exemption (DH Form 680 Part C)

- Can be rejected if clinical reasoning provided by physician is deemed to be invalid
- Each contraindicated vaccine must be listed, along with clinical reasoning for why **each** vaccine cannot be administered
- Section may only be signed by hand or e-signature in Florida SHOTS by a Florida-licensed physician

Florida Department of Health. School Immunization Guide. (2023)

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Non-Medical Exemption (DH Form 681)

- May only be used to document exemption from vaccination for **religious purposes**, not personal or philosophical purposes
- Form must be issued by county health department staff upon request
- No other information may be solicited from a parent other than what is indicated on the form, which is that a religious conflict with vaccination exists

Florida Department of Health. School Immunization Guide. (2023)

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Florida Vaccine Licensure Eligibility for Pharmacists

Educational Requirements	Liability Insurance	Protocol with Supervising Physician
• Initial 20-hour immunization administration certification program • 3 hours of approved CE for renewal	• Must be worth at least $200,000	• Must enter a protocol with a supervising physician to be eligible to immunize

Scope:
- Can immunize ages 7+
- Can administer any vaccine under adult and travel vaccination schedules released in 2022

Florida Department of Health. School Immunization Guide. (2023)

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Impacting Public Perceptions of Vaccination as a Pharmacist

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Challenging the Stigma Surrounding Vaccination: A Pharmacist's Role

<u>The Three C's of Vaccine Hesitancy</u>

- Complacency
- Convenience
- Confidence

Graham C. How to Address Vaccine Hesitancy. (2020)

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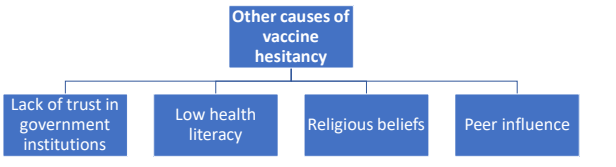
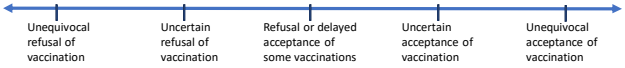
Challenging the Stigma Surrounding Vaccination: A Pharmacist's Role



Graham C. How to Address Vaccine Hesitancy. (2020)

55

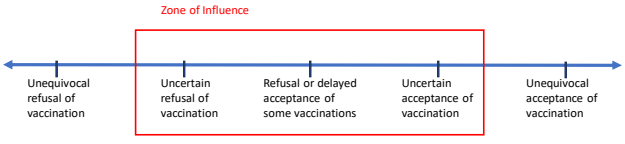
The Vaccine Hesitancy Continuum



Graham C. How to Address Vaccine Hesitancy. (2020)

56

The Vaccine Hesitancy Continuum



Graham C. How to Address Vaccine Hesitancy. (2020)

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Do's and Don'ts: Educating Parents with Vaccine Hesitancy

Do	Don't
• Listen to the patient and ask open-ended questions	• Criticize identities or groups to which the parent might belong, including vaccine-hesitant parents as a whole
• Avoid speaking in absolutes	• Repeat vaccine-related myths, even with the intent to dispel them
• Provide personal experiences with vaccinations	• Use fear as a motivational tactic
• Guide the patient towards acceptance, even if they do not change their mind immediately	• Provide an overabundance of information

Graham C. How to Address Vaccine Hesitancy. (2020)

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How Pharmacists Can Help

- Take advantage of accessibility
- Keep up with changes in recommendations
- Combat misinformation
- Advocate at the local and state level

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Question #2

What is a method pharmacists can employ to educate most parents with vaccine hesitancy?

a) Tell the parent that vaccines are mandatory for children per Florida law without a medical exemption

b) Determine the extent of a patient's hesitancy by asking open-ended questions

c) Provide the parent with randomized controlled trials supporting vaccine safety and efficacy

d) Refer the patient to a specialist

60

Question #2

What is a method pharmacists can employ to educate most parents with vaccine hesitancy?

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Question #3

Which of the following vaccine-preventable diseases has caused an outbreak to occur in South Florida within the past year?

a) Influenza

b) Diphtheria

c) Varicella

d) Measles

62

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63

Our Duty as Pharmacists

The Oath of a Pharmacist

"I promise to devote myself to a lifetime of service to others through the profession of pharmacy. In fulfilling this vow, I will consider the welfare of humanity and relief of suffering my primary concerns."

American Pharmacists Association. Oath of a Pharmacist. (2023)

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Thank You

Ethan Lobo, Pharm.D.
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Boca Raton Regional Hospital

January 26, 2025

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Rising Concerns with Under Vaccinated Children

Ethan Lobo, Pharm.D.
PGY-1 Pharmacy Resident
Boca Raton Regional Hospital
January 26, 2025

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They're Not Just Tiny Adults: Pediatric Update on Medication Management & Dosing Dilemmas

Emily N. Puchades, PharmD
PGY1 Pharmacy Resident
Nicklaus Children's Hospital
January 26th, 2025

1

Objectives

1. Describe how developmental stages impact pharmacokinetics (PK) and pharmacodynamics (PD), influencing drug absorption, distribution, metabolism, and excretion in pediatric populations.
2. Explain weight-based and body surface area (BSA) dosing strategies in pediatric patients.
3. Recognize the unique challenges in pediatric formulations and discuss strategies to optimize medication safety and efficacy.

2

Abbreviations

AE: Adverse Effect	eGFR: Estimated Glomerular Filtration Rate
AUC: Area Under the Curve	GI: Gastrointestinal
BBB: Blood Brain Barrier	HIV: Human Immunodeficiency Virus
BSA: Body Surface Area	HSV: Herpes Simplex Virus
CMV: Cytomegalovirus	PD: Pharmacodynamic
CNS: Central Nervous System	PK: Pharmacokinetic
CrCl: Creatinine Clearance	UGT: Uridine 5'-diphospho-glucuronosyltransferase
CYP: Cytochrome P450	Vd: Volume of Distribution
FDA: Food and Drug Administration	

3

Pediatric Age Definitions

Pediatric age stages according to the National Institute of Child Health and Human Development

- **Neonatal: Birth to < 28 days**
- **Infancy: ≥ 28 days to 12 months**
- **Toddler: 13 months to < 2 years**
- **Childhood: 2 years to 11 years**
- **Early Adolescence: 12 years to 18 years**
- **Late Adolescence/Early Adulthood: 19 years to 21 years**

3

Introduction

Pediatric patients have historically been regarded as "small adults" whose pharmacological management could be proportionally reduced as compared to adults

4

Introduction

Pediatric patients, and their medical management, differ from adults in several key aspects

- PK and PD parameters dynamically evolve and can significantly differ from one developmental era to another
- Fixed dosing is rarely used in pediatric management
- Palatable and easy-to-use formulations are a major aspect of medication coordination and decision making

5

Pharmacokinetics and Pharmacodynamics

28 Years Featuring
South Florida Pharmacy Residents

6

Pharmacokinetics and Pharmacodynamics

Pharmacokinetics: How the body interacts with administered substances or medications for the duration of exposure

- Different from pharmacodynamics
- "What the body does to the drug"
- Absorption, distribution, metabolism, and elimination

7

Pharmacokinetic Parameters

PK Parameter	Definition	Tissue Sites
Absorption	Movement of unchanged drug from the site of administration to systemic circulation	GI tract, skin, and pulmonary surfaces
Distribution	Reversible transfer of drug from blood to extravascular fluids and tissues	Adipose tissue, muscle, and the brain
Metabolism	Enzyme-mediated conversion of drugs into more soluble forms which can be easily excreted	Liver, kidneys, intestines, lungs, and blood
Elimination	Irreversible removal of drug from the body by several routes	Urine and feces

8

Absorption in Neonates

The neonatal period is characterized by:
- Neutral gastric pH
- Variable gastric emptying rates
- Immature biliary binding and transport
- Enhanced percutaneous absorption

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Absorption in Neonates

- Acid-labile medications such as Penicillin G experience enhanced absorption while acid-dependent medications such as proton pump inhibitors will experience suboptimal absorption
- Reduced biliary function results in low absorption of lipophilic drugs
- Topical medications, such as steroids and anesthetics, must be used with caution due to larger absorption rates

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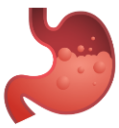
Absorption in Pediatrics

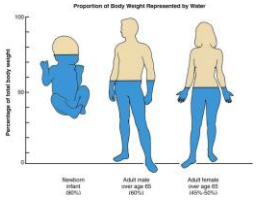
- GI function achieves adult activity by about 2 years of age
- Gastric pH becomes acidic, and the intestinal microbial environment grows in complexity by early childhood
- Enzymes required for intestinal absorption, such as p-glycoprotein (P-gp), reach adult levels of activity by 3 to 6 months of age



12

Distribution in Neonates

- Neonates have significantly more extracellular fluid and total body water
- Reduced presence of albumin and plasma proteins
  - Enhanced proportion of free drug
- The early neonatal period is also associated with an immature BBB
  - Enhanced distribution to brain tissue



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Distribution in Pediatrics

- Adipose tissue evolves throughout childhood and adolescence
  - Approximately 10% at birth and increases to 20% by 1 year of age
  - Then decreases to approximately 10 to 15% by late adolescence
- Vd of various drugs also fluctuates through development
  - DiazePAM (lipophilic medication), will have a Vd of 1.6 L/kg in neonates and 2.4 L/kg in children
- Outside of the neonatal period, lipophilic medications generally have a higher Vd, while hydrophilic medications have a lower Vd

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Knowledge Checkpoint #1

1. How does the developmental stage of a neonatal patient impact the distribution of gentamicin (hydrophilic medication) compared to a pediatric patient?

A) Neonates have less total body water, leading to a larger Vd for gentamicin and enhanced distribution

B) Neonates have more total body water, leading to a larger Vd for gentamicin and enhanced distribution

C) Neonates have less adipose tissue, which reduces gentamicin distribution

D) Neonates have less adipose tissue, which enhances gentamicin distribution

15

Knowledge Checkpoint #1

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D) Neonates have less adipose tissue, which enhances gentamicin distribution

16

Metabolism in Neonates

The development and activity of CYP enzymes and conjugation enzymes responsible for biotransformation occurs throughout the neonatal period

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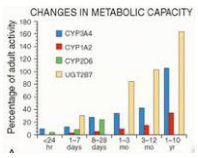
Metabolism in Neonates

- CYP enzymes begin to show activity at different stages throughout the neonatal period
- Interestingly, caffeine is a very commonly used medication in neonates and is metabolized by CYP1A2
  - Until the neonate's CYP activity reaches maturity, caffeine metabolism and clearance will be reduced as compared to that of an infant or child



18

Metabolism in Pediatrics

- Hepatic drug metabolism continues to evolve beyond the neonatal period
- Drugs metabolized via CYP enzymes require higher weight-based dosing throughout childhood due to enhanced hepatic clearance

19

Real-World Application: Phenytoin

- Due to enhanced activity of CYP2C9 and CYP2C19 in pediatrics, this patient population will typically require larger dosing of phenytoin as compared to adults

Focal onset seizures

Pediatric Dosing →

Maintenance therapy: IV, Oral: Initial: 5 mg/kg/day in divided doses (based upon dosage form, see below); usual range: 4 to 8 mg/kg/day; maximum daily dose: 300 mg/**day**. Some experts suggest higher maintenance doses (8 to 10 mg/kg/day) may be necessary in infants and young children [PR].

Usual dosing range [NR]:

6 months to 3 years: IV, Oral: 8 to 10 mg/kg/day.

4 to 6 years: IV, Oral: 7.5 to 9 mg/kg/day.

7 to 9 years: IV, Oral: 7 to 8 mg/kg/day.

10 to 16 years: IV, Oral: 6 to 7 mg/kg/day.

Adult Dosing →

Maintenance dose: **IV, Oral:** Initial: 4 to 7 mg/kg/day (usual 300 to 400 mg/day) given in 2 to 4 divided doses; adjust dose based on response and serum concentrations [PR]. Some experts recommend initiating maintenance therapy with 5 mg/kg/day in 2 divided doses [PR]. After an effective maintenance dose is established, may consider converting stable patients to once-daily dosing (ER capsule). A maximum dose has not been established; caution should be used in prescribing maintenance doses >600 mg/day. To ensure optimal absorption, individual oral doses should not exceed 400 mg [NR].

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Real-World Application: PHENobarbital

- Due to enhanced activity of CYP2C9 in pediatrics, this patient population will typically require larger dosing of PHENobarbital as compared to adults

Seizure Maintenance Therapy

Pediatric Dosing →

Seizures, maintenance therapy: Note: Maintenance dose usually starts 12 hours after loading dose: Dosage should be individualized based upon clinical response and serum concentration; once-daily doses usually administered at bedtime in children and adolescents.

Manufacturer's labeling: Infants, Children, and Adolescents: Oral: 3 to 6 mg/kg/day.

Alternate dosing: Limited data available [NR]:

Initial: Oral:

Infants and Children ≤5 years: 3 to 5 mg/kg/day in 1 to 2 divided doses.

Children >5 years and Adolescents: 2 to 3 mg/kg/day in 1 to 2 divided doses.

Adult Dosing →

Seizures: Maintenance dose:

Oral, IV: Usual dosage range (limited data available): 2 mg/kg/day in divided doses [PR]. **Note:** Dosage should be individualized based upon clinical response and serum concentration; 2 mg/kg/day typically produces a steady-state level of 20 mg/L [PR].

Manufacturer's labeling: **Oral:** Dosing in the prescribing information may not reflect current clinical practice. 60 to 200 mg/day **or** 50 to 100 mg 2 to 3 times daily.

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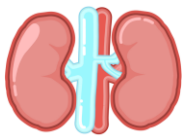
Elimination in Neonates and Pediatrics

- Renal excretion is mostly reduced throughout the neonatal period due to immature renal function
- GFR and tubular secretion do not reach adult activity until about 5 to 12 months of age.



Real-World Application: Fluconazole

- Fluconazole, a commonly used time-dependent anti-fungal, exhibits highly variable pharmacokinetics in pediatric patients
  - In children aged 2 to 12 years, fluconazole experiences a higher clearance as compared to adults as well as a larger Vd
    - Clearance: 0.03 L/kg/hr (pediatrics) vs. 0.016 L/kg/hr (adults)
    - Vd: 0.95 L/kg versus 0.7 L/kg
- Therefore, pediatric use of fluconazole requires higher dosing than adults

Real-World Application: Fluconazole

Oropharyngeal Candidiasis

Pediatric Dosing →

Candidiasis, oropharyngeal:

Treatment:

Infants and Children: Oral: 6 to 12 mg/kg/dose once daily for 7 to 14 days; maximum dose: 400 mg/dose.

Adolescents: Oral: 6 mg/kg/dose once daily for 7 to 14 days; usual adult dose: 100 to 200 mg/dose.

Adult Dosing →

Oropharyngeal:

Note: Reserve for moderate to severe disease, poor response to topical treatment, or recurrent infection.

IV, Oral: 200 mg on day 1, then 100 to 200 mg once daily for 7 to 14 days; some experts increase to 400 mg once daily for those who do not initially respond.

Age-Dependent Half-Lives →

Infants ≥9 months, Children, and Adolescents ≤13 years (single dose, oral): Mean range: 19.5 to 25 hours.

Children ≥5 years and Adolescents ≤15 years (multiple dose, IV): Mean range: 15.2 to 17.6 hours.

Adults: ~30 hours (range: 20 to 50 hours).

Older Adults ≥65 years: 46.2 hours.

Pharmacokinetics and Pharmacodynamics

Pharmacodynamics: the biochemical, physiologic, and molecular effects of drugs on the body

- Regarded as "what the drug does to the body"
- Involves receptor binding and sensitivity, post-receptor effects, and chemical interactions

9

Pharmacodynamics in Pediatrics

- The mechanisms of altered PD in pediatric patients continues to be poorly understood
- However, several examples of differing PD amongst developmental stages are known
  - Valproic acid has been seen to induce more hepatotoxicity in children
  - DiphenhydrAMINE CNS adverse effects are more common in infants
  - Adolescents experience more weight gain when initiated on anti-psychotic medications than adults

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Pediatric Dosing Strategies: Weight-Based and BSA-Based Dosing

DADE COUNTY PHARMACY ASSOCIATION
28 Years Featuring
South Florida Pharmacy Residents

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Pediatric Dosing Strategies

Pediatric dosing strategies do not follow a "one size fits all" approach and may vary widely depending on weight, height, BSA, body composition, organ development, and age.

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Knowledge Checkpoint #2

2. BSA is calculated using a patient's height and weight

A) True

B) False

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Knowledge Checkpoint #2

2. BSA is calculated using a patient's height and weight

A) True

B) False

Mosteller formula

$$BSA\ (m^2) = \sqrt{\frac{[\text{height (cm)} \times \text{weight (kg)}]}{3600}}$$

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Pediatric Dosing Strategies

Taylor et al., published in *Clinical Pharmacology and Therapeutics (2024)*	
Design	Systematic review evaluating the current landscape of dosing strategies in pediatrics
Methods	• Reviewed the package inserts of drugs approved after 2012 for use in pediatrics • Investigated how a pediatric patient's change in age, BSA, BMI, and body weight affected the AUC of ARIPiprazole, QUEtiapine, and asenapine
Results	• Most pediatric drugs utilized patient-specific parameters such as body weight, BSA, and age within their approved dosing strategies (continued on next slide) • Overall, the AUCs for ARIPiprazole, QUEtiapine, and asenapine decreased as body size increased (continued on next slide)
Conclusions	Pediatric patients experience much larger changes in growth and development over a shorter period as compared to adults. These periods of exponential growth translate to clinical changes in their pharmacokinetic abilities

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Pediatric Dosing Strategies

- A total of 370 approved drugs for use in pediatric patients were evaluated
  - 198 (53.5%) utilized body weight dependent dosing strategies
    - Mostly anti-infectives such as vancomycin and ceftriaxone
  - 32 (8.6%) utilized BSA dependent dosing strategies
    - Mostly antineoplastics such as cyclophosphamide
  - 22 (5.9%) utilized age dependent dosing strategies
    - Mostly CNS agents such as valproic acid

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Real-World Application: ValGANciclovir

- ValGANciclovir, an antiviral agent used for the prevention and treatment of CMV, has extensive literature detailing the extrapolation from flat adult dosing to BSA-dependent pediatric dosing
- In current practice, valGANciclovir dosing in pediatrics is based on BSA and renal function as shown below:

Dose (mg) = 7 x BSA x CrCl *(utilizing modified Schwartz formula)*

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Real-World Application: ValGANciclovir

Vaudry et al., published in *American Journal of Transplantation* (2009)	
Design	Multicenter, open-label, noncomparative study evaluating the safety and pharmacokinetic profile of oral valGANciclovir in pediatrics solid organ transplant patients
Objectives	• Provide *in vivo* data to validate the BSA and CrCl-based dosing strategy utilized for pediatric valGANciclovir • Expand on previous literature which investigated valGANciclovir BSA-based dosing and revealed that the lack of renally-based dosing yielded subtherapeutic levels in children < 5 years of age
Methods	• Once-daily dosing of prophylactic valGANciclovir starting on day 2 post-transplant until day 100 post-transplant • Patients were monitored for 26 weeks post-transplantation and valGANciclovir serum levels were obtained once after at least 3 doses • Dosing based on BSA and renal function ○ ***Schwartz equation for eGFR = [k x height (cm)] / SCr (mg/dL)*** ▪ K: age-dependent constant value

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Real-World Application: ValGANciclovir

Vaudry et al., published in *American Journal of Transplantation* (2009)	
Safety and Efficacy Results	• 63 patients were enrolled in the study • 94% of patients experienced at least one AE and 93% of those AEs were found to be unrelated to valGANciclovir therapy • Opportunistic infections occurred in six patients while receiving valGANciclovir ▪ Oral candidiasis (2), abdominal candidiasis (1), oral HSV (1), and CMV (2) • Four cases of treatment failure ▪ Defined as CMV disease requiring treatment or study discontinuation ▪ Two patients developed CMV which required treatment at Day 8 and Day 86, respectively ▪ Two patients discontinued the study due to toxicities • Five patients contracted CMV after 100 days of valGANciclovir

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Real-World Application: ValGANciclovir

Vaudry et al., published in *American Journal of Transplantation* (2009)	
Pharmaco-kinetic Results	• Serum valGANciclovir sampling and pharmacokinetic profiling revealed that BSA and valGANciclovir AUC have an inverse relationship • The highest AUC was observed when CrCl ≥ 150 mL/min/1.73 m^2 and the lowest AUC when CrCl was between 110 – 149 mL/min/1.73 m^2
Conclusions	• This study supported the integration of renal function and led to the validation of our current practice • No age group was significantly under or over-dosed throughout the study • The observed AUC levels were similar to those that are safe and effective in adult patients

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Pediatric Formulations: Challenges and Safety Concerns

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Pediatric Formulation Challenges

Aside from significant differences in PK, PD, and dosing strategies, pediatric patients also require specialized drug formulations to achieve successful pharmacological therapy

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Knowledge Checkpoint #3

3. What is one common challenge with pediatric drug formulations that can affect medication safety and efficacy?

A) Pediatric patients require much higher doses of medication due to faster metabolism.

B) Many pediatric medications lack liquid formulations, making dosing difficult for young children.

C) Pediatric medications are often formulated as chewable tablets, which can cause choking hazards.

D) Pediatric patients often experience decreased renal clearance, increasing the risk of toxicity.

36

Knowledge Checkpoint #3

3. What is one common challenge with pediatric drug formulations that can affect medication safety and efficacy?

A) Pediatric patients require much higher doses of medication due to faster metabolism.

B) Many pediatric medications lack liquid formulations, making dosing difficult for young children.

C) Pediatric medications are often formulated as chewable tablets, which can cause choking hazards.

D) Pediatric patients often experience decreased renal clearance, increasing the risk of toxicity.

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Pediatric Formulation Challenges

- Pediatric patients require distinct and specialized formulation considerations due to
  - Difficulty swallowing tablets and capsules
  - Adherence issues with unpalatable medications
  - Potential toxicities with excipients that are safe for adults
  - Cognitive and psychological obstacles associated with administration of medications

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Pediatric Formulation Challenges

- Pediatric formulation challenges can significantly impact treatment success and enhance the risk of negative clinical outcomes
- Unfortunately, the road to appreciating these formulation considerations and proactively providing child-friendly medications has been paved by several formulation-related injuries and fatalities

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Pediatric Formulation Challenges

- Clinical consequences include:
  - Infant deaths from choking on tablets and capsules
  - Benzyl alcohol and diethylene glycol poisoning from sulfonamide elixirs
  - Electrolyte disturbances due to parenteral medications compounded with high sodium and potassium concentrations which are otherwise safe in adults
  - Overdosing due to drawing up doses at home by caretakers

Caution With Excipients

- The Inactive Ingredient List published by the FDA has not been validated for pediatric patients
- No established "safe and appropriate" excipient intake levels and literature evaluating the safety of excipients in pediatric patients is scant
- Neonates are especially at risk for excipient-related toxicities

Real-World Application: Lopinavir/Ritonavir

- Lopinavir/ritonavir (Kaletra) is available in an oral solution and used to manage HIV in patients 14 days or older
- Oral solution contains alcohol and propylene glycol which may cause cardiac, renal, and respiratory toxicities in high levels

Real-World Application: Lopinavir/Ritonavir

- Prior to 2011, labeling did not exclude patients younger than 14 days old from use
  - High incidence of propylene glycol toxicities in neonatal patients
- In 2011, the FDA modified labeling to include a new warning against use in the time between birth and 14 days of life

Real-World Application: Lopinavir/Ritonavir

WARNINGS AND PRECAUTIONS

The following have been observed in patients receiving KALETRA:

- The concomitant use of KALETRA and certain other drugs may result in known or potentially significant drug interactions. Consult the full prescribing information prior to and during treatment for potential drug interactions. (5.1, 7.3)
- Toxicity in preterm neonates: KALETRA oral solution should not be used in preterm neonates in the immediate postnatal period because of possible toxicities. A safe and effective dose of KALETRA oral solution in this patient population has not been established. (2.3, 5.2).

Obtained from KALETRA Prescribing Information
www.accessdata.fda.gov

Lack of Formulation-Based Data

- It is known that pediatric drug trials are uncommon
- Published pediatric drug trials should report formulation and method of administration information to enhance reproducibility, reliability, and validity

Lack of Formulation-Based Data

- A systematic review conducted by Standing et al., and published in *Pediatrics* evaluated the reporting of formulation information in drug trials investigating oral medications in patients 12 years and younger
- Data was compiled from 76 articles published between July 2002 and June 2004 from several journals including *New England Journal of Medicine*, *Journal of the American Medical Association*, *Lancet*, *British Medical Journal*, and *Pediatrics*

Lack of Formulation-Based Data

- Most of the studies did not provide the full scope of information required for reproducibility
  - 26% of the studies did not state the formulation used
  - 19 of the studies used tablets or capsules but only 5 of them detailed administration strategies
  - 1 study provided an alternative formulation for participants unable to swallow medications
  - 6 studies used tablets/capsules in patients < 4 years of age but did not provide dosing information

Lack of Formulation-Based Data

- The lack of clear formulation and dosing guidance provided by reputable medical journals highlights the urgent need for improved formulation reporting in pediatric literature to serve as a reliable basis for accurate and innovative pharmacological management

Innovative Dosage Form Technology

As a result of the documented safety concerns regarding pediatric drug formulations, several novel technologies have been developed to achieve safe and effective medication delivery

Innovative Dosage Form Technology

- Orodispersable mini-tablets and films
  - Allow for rapid and complete disintegration in the mouth thereby eliminating the need for swallowing
  - Manufacturers are compounding medications such as ondansetron, valproic acid, and risperiDONE into these formulations

Innovative Dosage Form Technology

- XStraw ® delivery system
  - Straw device pre-filled with drug and allows patient to easily swallow drug while drinking water or juice (if appropriate)

Conclusion and Takeaways

- Pediatric patients require highly specialized and dedicated dosing considerations due to their evolving PK and PD profiles, propensity to under and overdosing, and sensitivity to commercially available dosing formulations and excipients
- The need for clear, reliable, and reproducible pediatric drug trials still exists and poses an obstacle to ideal pharmacological management

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Thank You!

Questions?

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Are You Ready for It? Pediatric Emergency Management

Cristella Figueroa, PharmD
PGY1 Pharmacy Resident
Nicklaus Children's Hospital
Miami, FL
January 26, 2025

29 Years Featuring
South Florida Pharmacy Residents

Objectives

1. Recognize and manage status asthmaticus and status epilepticus in pediatric patients
2. List essential medications and their roles in pediatric resuscitation and emergency care
3. Describe the appropriate selection of medications for Rapid Sequence Intubation (RSI)
4. Explain the pharmacist's role in managing medications and ensuring patient safety during pediatric emergency situations

Abbreviations

ICP: increased intracranial pressure
IM: intramuscular
IN: intranasal
IO: intraosseous
IV: intravenous
IVP: intravenous push
kg: kilograms
mcg: micrograms
mg: milligrams
mL: milliliters
PE: phenytoin equivalent
PICU: pediatric intensive care unit
PO: by mouth
PR: per rectum

Status Asthmaticus

Defined as an acute asthma exacerbation that does not respond to standard management that may lead to respiratory failure

Schroeder AR, et al. *American Academy of Pediatrics Textbook of Pediatric Care* 2018;1:372

Pathophysiology

- Key components:
  - Bronchial smooth muscle spasm
  - Airway inflammation
  - Increased mucous production
  - Impaired gas exchange
  - Increased work of breathing

Dewitt TH, et al. *Quick Reference* 2022.
Image: https://www.myamericannurse.com/understanding-asthma-pathophysiology/

Supportive Management

- **Oxygen**
  - Goal is to maintain saturations > 90%
  - Monitor with pulse oximetry
- **Hydration**
  - Goal is to restore or maintain euvolemia
  - Provide IV normal saline or Lactated Ringer's solution as a bolus of a maximum 20 mL/kg or 1000 mL over 1 hour

Carroll CL, et al. *Crit Care Clin.* 2013;29(2):353-368.
Global Initiative for Asthma (GINA). "Global Strategy for Asthma Management and Prevention." 2016; 171.

First-Line Management

Albuterol Sulfate

Mechanism of Action	Short-acting beta-2 agonist that acts as a bronchodilator
Nebulization	2.5 or 5 mg every 20 minutes for 3 doses 7.5 or 15 mg over 1 hour
Inhaler	4 or 8 puffs every 20 minutes for 2 to 3 doses

Global Initiative for Asthma (GINA). "Global Strategy for Asthma Management and Prevention." 2024; 173.
Schroeder AR, et al. American Academy of Pediatrics Textbook of Pediatric Care. 2016; 172.

Supplemental Management

Ipratropium Bromide

Mechanism of Action	Short-acting muscarinic receptor antagonist that acts a bronchodilator
Nebulization	250 or 500 mcg every 20 minutes for 1 hour
Inhaler	4 or 8 puffs every 20 minutes for up to 3 hours

Albuterol Sulfate + Ipratropium Bromide (DuoNeb)

- Optimize bronchodilation and reduce airway resistance

Global Initiative for Asthma (GINA). "Global Strategy for Asthma Management and Prevention." 2024; 158, 174.
Schroeder AR, et al. American Academy of Pediatrics Textbook of Pediatric Care. 2016; Chapter 172.

Supplemental Management

Corticosteroids

Mechanism of Action	Reduces inflammation and bronchoconstriction by increasing beta receptor density on bronchial smooth muscle cells
Methylprednisolone	Loading dose: 2 mg/kg IV, then 0.5 to 1 mg/kg/dose every 6 hours Maximum 80 mg/day

Global Initiative for Asthma (GINA). "Global Strategy for Asthma Management and Prevention." 2024; 201.
Schroeder AR, et al. American Academy of Pediatrics Textbook of Pediatric Care. 2016; Chapter 172.

Supplemental Management

Corticosteroids

Dexamethasone	0.6 mg/kg PO/IV/IM once Maximum 16 mg/dose
Prednisolone	1 to 2 mg/kg PO once Maximum 60 mg/day
Prednisone	1 to 2 mg/kg PO once Maximum 60 mg/day

Global Initiative for Asthma (GINA). "Global Strategy for Asthma Management and Prevention." 2024; 201.
Schroeder AR, et al. American Academy of Pediatrics Textbook of Pediatric Care. 2018; Chapter 372.

When to Admit?

Indications for PICU admission
- Requires pressure ventilation, sedation, or continuous IV bronchodilator infusions

Schroeder AR, et al. American Academy of Pediatrics Textbook of Pediatric Care. 2018; 372.

Status Epilepticus

Defined as 5 minutes or more of continuous clinical and/or electrographic seizure activity or recurrent seizure activity without recovery between seizures

Brophy GM, et al. Neurocrit Care. 2012; 17(1):3-23.

Seizures

Definition

Defined as a transient occurrence of abnormal excessive or synchronous neuronal electrical activity of the brain

Etiology

- Metabolic disturbances
- Central nervous system infections
- Traumatic brain injury
- Drug complications
- Hypoxia
- Fevers

Brophy GM, et al. Neurocrit Care. 2012;17(1):3-23.

Types

Generalized Convulsive Status Epilepticus (GCSE)

Defined as convulsions associated with rhythmic jerking of the extremities

Characteristics:

- Generalized tonic-clonic movements of the extremities
- Mental status impairment
- Focal neurologic deficits in the post-ictal period

Brophy GM, et al. Neurocrit Care. 2012;17(1):3-23.

Types

Non-Convulsive Status Epilepticus (NCSE)

Defined as seizure activity seen on an EEG without clinical findings associated with GCSE

Characteristics include:

- "Wandering confused" patient
- Acutely ill with severely impaired mental status, with or without subtle motor movements, staring spells

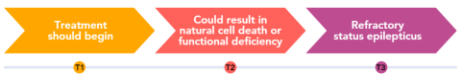
Brophy GM, et al. Neurocrit Care. 2012;17(1):3-23.

Prognosis

	GCSE	NCSE
Mortality	At hospital discharge: 9-21% At 30 days: 19-27% At 90 days: 19% SE develops: 65%	At hospital discharge: 18-**52%** At 30 days: **65%** SE develops: 75%
Morbidity	Severe neurologic or cognitive sequalae: 11-16% Deterioration of functional status: 23-26%	

Brophy GM, et al. Neurocrit Care. 2012;17(1):3-23.

Time is Brain



Defined as status epilepticus that does not respond to the standard treatment of benzodiazepines followed by an antiepileptic drug (AED)

Brophy GM, et al. Neurocrit Care. 2012;17(1):3-23.

Stabilization Phase: 0 – 5 minutes

- Stabilize patient
  - Airway
  - Breathing
  - Circulation
- Time seizure
- Initiate EEG
- Obtain fingerstick glucose
- Vascular access

Brophy GM, et al. Neurocrit Care. 2012;17(1):3-23.
Glauser T, et al. Epilepsy Curr. 2006;6(1):1-9.

Initial Therapy Phase: 5 – 20 minutes

Benzodiazepines

Mechanism of Action	GABA receptor agonist
Lorazepam	0.1 mg/kg/dose slow IV Maximum 4 mg/dose Rate to not exceed 2 mg/minute or 0.05 mg/kg over 2 to 5 minutes

Brophy GM, et al. *Neurocrit Care*. 2012;17(1):3-23.
Glauser T, et al. *Epilepsy Curr*. 2016;16(1):48-61.

Initial Therapy Phase: 5 – 20 minutes

Benzodiazepines

Midazolam	0.2 mg/kg/dose IM once Maximum 10 mg/dose
Diazepam	0.15 to 0.2 mg/kg/dose slow IV Maximum 10 mg/dose May repeat dose once in 5 minutes Rate to not exceed 5 mg/min

Brophy GM, et al. *Neurocrit Care*. 2012;17(1):3-23.
Glauser T, et al. *Epilepsy Curr*. 2016;16(1):48-61.

Initial Therapy Phase: 5 – 20 minutes

Alternative Options

Midazolam	0.2 mg/kg/dose IN once Maximum 10 mg/dose

Brophy GM, et al. *Neurocrit Care*. 2012;17(1):3-23.
Glauser T, et al. *Epilepsy Curr*. 2016;16(1):48-61.

Initial Therapy Phase: 5 – 20 minutes

Alternative Options

Diazepam	2 to 5 years: 0.5 mg/kg/dose PR 6 to 11 years: 0.3 mg/kg/dose PR ≥ 12 years: 0.2 mg/kg/dose PR Maximum 20 mg/dose

Brophy GM, et al. *Neurocrit Care*. 2012;17(1):3-23
Glauser T, et al. *Epilepsy Curr*. 2016;16(1):48-61

Second Therapy Phase: 20 – 40 minutes

Longer-Acting Options

	Mechanism of Action
Fosphenytoin	Sodium channel blocker
Valproic Acid	GABA receptor agonist
Levetiracetam	Calcium channel blocker and GABA receptor agonist

Brophy GM, et al. *Neurocrit Care*. 2012;17(1):3-23
Glauser T, et al. *Epilepsy Curr*. 2016;16(1):48-61
Kapur J, et al. *N Engl J Med*. 2019;381(22):2103-2113

Second Therapy Phase: 20 – 40 minutes

Longer-Acting Options

Fosphenytoin	20 mg PE/kg/dose IV once over 15 minutes Maximum 1500 mg/dose Rate of 2 mg PE/kg/min up to 150 mg PE/min
Valproic Acid	40 mg/kg/dose IV once over 15 minutes Maximum 3000 mg/dose Rate of 1.5 to 4 mg/kg/min up to 100 mg/min
Levetiracetam	60 mg/kg/dose IV once over 5 to 10 minutes Maximum 4500 mg/dose

Brophy GM, et al. *Neurocrit Care*. 2012;17(1):3-23
Glauser T, et al. *Epilepsy Curr*. 2016;16(1):48-61

The ESETT Trial

Randomized Trial of Three Anticonvulsant Medications for Status Epilepticus	
Design	Randomized, blinded, adaptive trial comparing the efficacy and safety of intravenous levetiracetam, fosphenytoin, and valproic acid
Methods	Children and adults with convulsive status epilepticus that were unresponsive to treatment with benzodiazepines were assigned to receive one of three anticonvulsive agents
Results	At 60 minutes 68 of 145 (47%) in the levetiracetam group, 53 of 118 (45%) in the fosphenytoin group, and 56 of 121 (46%) in the valproic acid group had cessation of status epilepticus
Conclusion	All three agents led to seizure cessation and improved alertness by 60 minutes in approximately half the patients in each group, and were associated with similar incidences of adverse events

Kapur J, et al. *N Engl J Med* 2019;381(22):2103-2113.

Third Therapy Phase: 40 – 60 minutes

Refractory Status Epilepticus (RSE)

- Defined as no response to standard treatment regimens for status epilepticus
  - Guidelines consider RSE after a failure of an adequately dosed initial benzodiazepine and one antiepileptic drug
- Consider repeat bolus doses of previous drug therapy or initiate additional agents via continuous infusion

Brophy GM, et al. *Neurocrit Care* 2012;17(1):3-23.
Glauser T, et al. *Epilepsy Curr* 2016;16(1):48-61.

Third Therapy Phase: 40 – 60 minutes

Continuous Infusions

Midazolam	0.2 mg/kg/dose IV at a rate of 2 mg/min, then 0.05 to 2 mg/kg/h continuous infusion May increase rate by 0.05 to 0.1 mg/kg/h every 3 to 4 hours
Propofol	20 mcg/kg/min with 1 to 2 mg/kg loading dose, then 30 to 200 mcg/kg/min continuous infusion
Pentobarbital	5 to 15 mg/kg at a rate $\leq$ 50 mg/min, then 0.5 to 5 mg/kg/h continuous infusion

Brophy GM, et al. *Neurocrit Care* 2012;17(1):3-23.
Glauser T, et al. *Epilepsy Curr* 2016;16(1):48-61.

Knowledge Checkpoint 1

Which of the following medications is most appropriate for the initial intravenous treatment of status epilepticus in a pediatric patient?

a. Lorazepam
b. Levetiracetam
c. Phenobarbital
d. Fosphenytoin

Knowledge Checkpoint 1

Which of the following medications is most appropriate for the initial intravenous treatment of status epilepticus in a pediatric patient?

a. Lorazepam
b. Levetiracetam
c. Phenobarbital
d. Fosphenytoin

Pediatric Resuscitation

Emergency medical procedures used to manage a child experiencing cardiac or respiratory arrest

Topjian AA, et al. *Circulation*. 2020;142:S469-S523.

Etiology

Respiratory Arrest

- Upper airway obstruction
- Lower airway obstruction
- Lung tissue disease
  - Parenchymal
- Disordered breathing

Topiken AA, et al. *Circulation*. 2021;143:1569-1573.

Etiology

Shock

- Hypovolemic
  - Hemorrhagic
  - Non-hemorrhagic
- Distributive
  - Sepsis
  - Anaphylaxis
  - Neurogenic
- Cardiogenic
  - Congenital heart disease
  - Myocarditis
- Obstructive
  - Cardiac tamponade
  - Tension pneumothorax
  - Pulmonary embolism

Topiken AA, et al. *Circulation*. 2021;143:1569-1573.

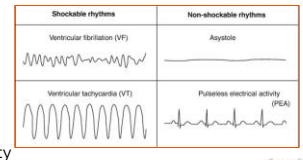
Rhythms

Shockable

- Ventricular fibrillation
- Ventricular tachycardia

Non-Shockable

- Asystole
- Pulseless electrical activity



Topiken AA, et al. *Circulation*. 2021;143:1569-1573.
Image: https://www.osmosis.com/nursing/study-guides/pediatric-considerations-1-698832952

Pediatric Resuscitation

Pediatric cardiac arrest algorithm from the American Heart Association

Topjian AA, et al. *Circulation* 2020;142:S469-S523

Reversible Causes of Cardiac Arrest

H's & T's

- Hypovolemia
- Hypoxia
- Hydrogen ions (acidosis)
- Hypoglycemia
- Hypokalemia
- Hyperkalemia
- Hypothermia
- Tension pneumothorax
- Tamponade (cardiac)
- Toxins
- Thrombosis – pulmonary
- Thrombosis – coronary

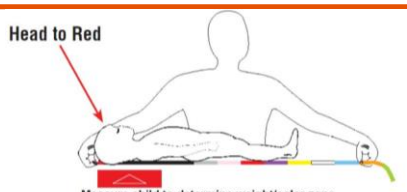
Topjian AA, et al. *Circulation* 2020;142:S469-S523

Pediatric Code Carts

- Pediatric code carts use a color-coded system to categorize medications and supplies by weight groups
- A child's weight can be estimated in an emergency using Broselow-Luten Tape

Topjian AA, et al. *Circulation* 2020;142:S469-S523

Broselow-Luten Tape



Measure child to determine weight/color zone.
If a child appears overweight consider utilizing one zone higher for dosing only. Always use the reference tape measured length zone for equipment selection regardless of body habitus.

http://www.jems.com/patient-care/emergency-medical-care/a-look-at-two-types-broselow-luten-tape-2015-vs-2017

Broselow-Luten Tape

http://www.jems.com/patient-care/emergency-medical-care/a-look-at-two-types-broselow-luten-tape-2015-vs-2017

Common Medications

Adenosine	Diphenhydramine	Methylprednisolone
Amiodarone	Epinephrine	Naloxone
Atropine	Furosemide	Normal Saline
Calcium Chloride	Lidocaine	Sodium Bicarbonate
Dextrose	Magnesium Sulfate	Sterile Water

Cardiac Arrest Drug Therapy

Epinephrine

Mechanism of Action	Alpha-1, Beta-1, Beta-2 agonist
Dose	0.01 mg/kg (0.1 mL/kg) IV/IO of 0.1 mg/mL solution Maximum 1 mg/dose Repeat every 3 – 5 minutes If no IV/IO access, may give endotracheal dose • 0.1 mg/kg (0.1 mL/kg) of 1 mg/mL solution • Maximum 2.5 mg/dose

Cardiac Arrest Drug Therapy

Amiodarone

Mechanism of Action	Class III anti-arrhythmic that inhibits adrenergic stimulation and inhibits potassium, calcium, and sodium channels
Dose	5 mg/kg IV/IO rapid bolus Maximum 300 mg/dose May repeat up to 3 total doses for refractory VF or pulseless VT

Cardiac Arrest Drug Therapy

Lidocaine

Mechanism of Action	Class Ib anti-arrhythmic that inhibits sodium channels
Dose	Loading dose 1 mg/kg IV/IO, then 20 to 50 mcg/kg/minute continuous infusion May repeat bolus if delay between initial and start of infusion is greater than 15 minutes Maximum cumulative dose 300 mg within 1 hour

Pediatric Subtleties

- Variations in code medications
  - Sodium bicarbonate
- Earlier resuscitation intervention
  - Start compressions at heart rates less than 60 beats per minutes
- Atropine administration

Cardiac Arrest Drug Recap

0.1 mL/kg

5 mg/kg

1 mg/kg

Knowledge Checkpoint 2

During pediatric cardiac resuscitation, what is the dose of epinephrine?

a. 0.01 mg/kg
b. 0.05 mg/kg
c. 0.75 mg/kg
d. 1 mg/kg

Knowledge Checkpoint 2

During pediatric cardiac resuscitation, what is the dose of epinephrine?

a. 0.01 mg/kg
b. 0.05 mg/kg
c. 0.75 mg/kg
d. 1 mg/kg

Rapid Sequence Intubation (RSI)

Process of establishing a safe and functional respiratory system in patients who are unable to breathe on their own

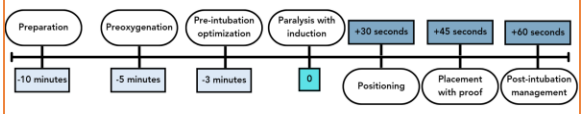
Hampton JP, et al. Am J Health Sys Pharm 2023;80(4):180-195.

The 7P's

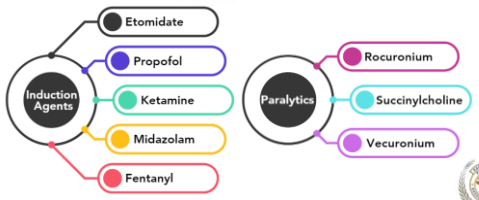
Hampton JP, et al. Am J Health Sys Pharm 2023;80(4):180-195.

The 7P's

Successful intubation is usually accomplished within 10 minutes of the decision to intubate the patient



Induction & Paralysis



Induction Agents

Etomidate

Mechanism of Action	GABA receptor agonist
Dose	0.2 to 0.4 mg/kg/dose IVP Maximum 20 mg/dose
Onset	30 to 60 seconds
Duration	2 to 3 minutes

- Hemodynamically neutral
- Useful in those with ICP
- Avoid in those with sepsis

Induction Agents

Propofol

Mechanism of Action	GABA receptor agonist
Dose	1 to 2 mg/kg/dose IVP Maximum 100 mg/dose
Onset	10 to 60 seconds
Duration	3 to 10 minutes

- May be used in those with seizures
- May cause hypotension
- Egg, soy, peanut allergies are no longer a contraindication

Induction Agents

Ketamine

Mechanism of Action	NMDA receptor antagonist
Dose	1 to 2 mg/kg/dose IVP
Onset	30 to 60 seconds
Duration	5 to 10 minutes

- Preferred in those with septic shock
- Consider in patients who are hypotensive, volume depleted, or hemodynamically unstable
- Consider avoiding in those with ICP

Induction Agents

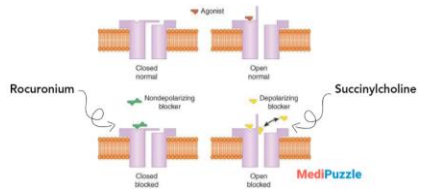
Midazolam

Mechanism	GABA receptor agonist
Dose	0.1 mg/kg/dose IVP (range 0.1 to 0.3 mg/kg)
Onset	10 to 60 seconds
Duration	30 to 45 minutes

Fentanyl

Mechanism	Mu-opioid receptor agonist
Dose	1 mcg/kg/dose IV (maximum 50 mcg/dose)
Onset	10 to 60 seconds
Duration	15 minutes

Neuromuscular Blockade



http://medpuzzle.com/blog/v20

Paralytic Agents

Rocuronium

Mechanism of Action	Non-depolarizing neuromuscular blocking agent
Dose	1 mg/kg IVP (maximum 100 mg/dose)
Onset	60 seconds
Duration	40 to 60 minutes

- Use ideal body weight if available
- Longer duration of paralysis
- Effects may be reversed with sugammadex
- Preferred when succinylcholine use is contraindicated

Hampton JP, et al. Am J Health Syst Pharm. 2023;80(4):182-195.

Paralytic Agents

Succinylcholine

Mechanism of Action	Depolarizing neuromuscular blocking agent
Dose	1 to 1.5 mg/kg IVP (maximum 200 mg/dose)
Onset	45 seconds
Duration	10 minutes

- Use actual body weight
- Contraindicated in neuromuscular disorders, hyperkalemia, personal or family history of malignant hyperthermia

Hampton JP, et al. Am J Health Syst Pharm. 2023;80(4):182-195.

Post-Intubation Management

Ongoing sedation and analgesia should be maintained

Sedation	Analgesia
Dexmedetomidine	Fentanyl
Ketamine	Hydromorphone
Midazolam	Morphine
Propofol	

Hampton JP, et al. Am J Health Sys Pharm 2023;80(4):180-195.

Points to Remember

- Ensure the induction agent is administered and starts working before the paralytic is administered
- Ensure post-intubation sedation is started as soon as possible
- Keep math simple:
  - Dose etomidate at one-third the weight
  - Round doses for easier calculations

Hampton JP, et al. Am J Health Sys Pharm 2023;80(4):180-195.

Knowledge Checkpoint 3

Which of the following is a depolarizing neuromuscular blocking agent?

a. Rocuronium
b. Succinylcholine
c. Vecuronium
d. Cisatracurium

Knowledge Checkpoint 3

Which of the following is a depolarizing neuromuscular blocking agent?

a. Rocuronium
b. Succinylcholine
c. Vecuronium
d. Cisatracurium

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Pharmacist's Role in the ED

- Formally recognized in February 2020 as a specialty practice area
- Integral to the safety and care of ED patients
  - Anticipate pharmacotherapy needs
  - Timely medication administration
  - Optimization of therapy
  - Medication safety

Farmer BM, et al. *J Med Toxicol*. 2018;14(1):114-116.

62

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Questions?

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Less is Better: Negative Effects of Lifetime Doses of Corticosteroids

Celine Wong, PharmD.
Jackson Memorial Hospital
Miami, Florida
January 26, 2025

29 Years Featuring
South Florida Pharmacy Residents

1

Objectives

- Identify corticosteroids and their therapeutic applications
- Analyze the mechanisms of actions of corticosteroids
- Discuss the potential long-term side effects of corticosteroid therapy
- Identify strategies for mitigating adverse effects of long-term corticosteroid use
- Evaluate a patient exhibiting adverse reactions from corticosteroid treatment

2

Case Report

- A 55-year-old female patient was admitted to the general medicine department with complaints of facial puffiness for one year, neck pain for three days, giddiness, headache, eye pain, exertional dyspnea, generalized weakness, decreased sleep, and constipation.
- **Past Medical History**: Hypothyroidism, hypertension, right knee pain
- **Home Medications:** levothyroxine 25mcg, telmisartan/hydrochlorothiazide 40mg/2.5mg, dexamethasone 0.5 mg
- **Physical Examination**: facial puffiness +ve, buffalo hump , B/L pitting type of edema
- **Imaging:** Ultrasound Abdomen showed fatty changes in liver and hepatomegaly

Polubabari SK, Sridevi OK. *Journal of Drug Delivery and Therapeutics*. 2022.

3

Case Report

Parameter	Value
Random blood glucose	270 mg/dL (H)
Fasting blood glucose	166 mg/dL (H)
HbA1c	7.4% (H)
Total cholesterol	305 mg/dL (H)
High-Density Lipoprotein	59 mg/dL (L)
Low-Density Lipoprotein	179 mg/dL (H)
Very Low-Density Lipoprotein	6.6 mg/dL
Triglycerides	277 mg/dL (H)
25-Hydroxy Vit D test	13.69 ng/mL (L)

Poludasu et al. *Journal of Drug Delivery and Therapeutics*. 2022.

4

Corticosteroids

5

What are Corticosteroids?

- Corticosteroids: a class of steroid hormones that regulate cellular functions
- These steroid hormones are synthesized and released by the adrenal glands in response to physiological cues and stress and are regulated by the hypothalamic-pituitary-adrenal (HPA) axis.

McKay LI. *Cancer Medicine*. 6th edition. Hamilton (ON): BC Decker; 2003.

6

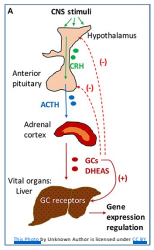
Hypothalamic-Pituitary-Adrenal (HPA) Axis

The autonomic nervous system triggers the hypothalamus to release corticotrophin-releasing hormone (CRH) and arginine vasopressin (AVP)

CRH and AVP triggers the corticotroph cells in the pituitary to secrete adrenocorticotrophin hormone (ACTH)

ACTH acts on the adrenal cortex to stimulate the synthesis and release of cortisol

Cortisol access target tissues to regulate a myriad of physiologic processes



McKay U. *Cancer Medicine*. 6th edition. Hamilton (ON): BC Decker; 2003.

7

Mechanisms of Action

Corticosteroid Activity

Glucocorticoid Effects

Mineralocorticoid Effects

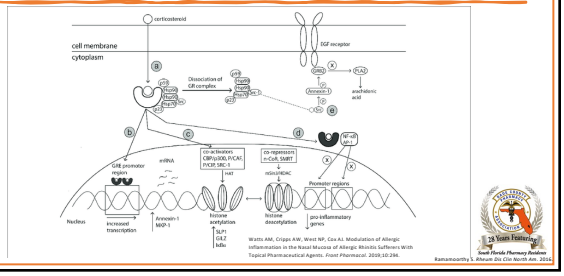
Inflammation, Immunity, Wound Healing, Metabolism, etc.

Salt, Water, and Mineral Metabolism

McKay U. *Cancer Medicine*. 6th edition. Hamilton (ON): BC Decker; 2003.

8

Glucocorticoid Effects



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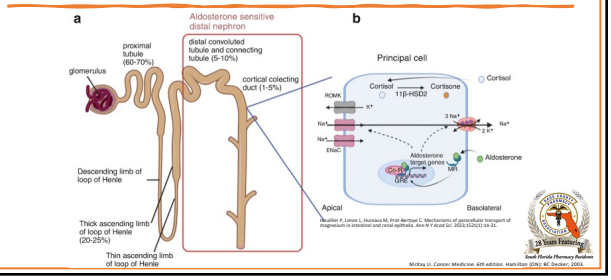
9

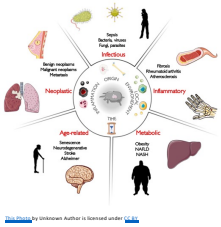
Mineralocorticoid Effects



10

Clinical Uses of Corticosteroids

Asthma	Psoriasis	Allergies
Post-Transplant Immune Suppression	Adrenal Insufficiencies	Septic Shock
Rheumatoid Arthritis	Inflammatory Bowel Disease	Multiple Sclerosis



Ramsammarthy S, Cidlowski JA. Rheum Dis Clin North Am. 2016.

11

Systemic Corticosteroids

Drug	Dosing	Activity*	Equivalent Dose
Cortisone	**Oral:** 20-300 mg/day in 2-3 divided doses	M=G	25 mg
Hydrocortisone (Solu-Cortef®, Cortef®)	**Oral:** 10-25 mg/day in 2-3 divided doses **IV/IM:** 100-150 mg/day in 2-3 divided doses	M=G	20 mg
Fludrocortisone	**Oral:** 0.05-0.2 mg/day in 1-2 divided doses	M>>>G	0.1 mg
Prednisone (Prednisone Intensol®, Rayos®)	**Oral:** 10-60 mg/day once daily or 2-4 divided doses, 1-1.5 mg/kg/day	M<<G	5 mg
Prednisolone (Millipred®)	**Oral:** 10-60 mg/day once daily or in 2-4 divided doses, 1-1.5 mg/kg/ day	M<<G	5 mg
Methylprednisolone (Medrol®, Solu-Medrol®, Depo-Medrol®)	**Oral:** 16-64 mg/day once daily or divided **IV:** 40-125 mg/day once daily or divided **IM:** 40-60 mg as a single dose	M<<G	4 mg
Triamcinolone (Kenalog®)	**Intra-articular:** 10, 30, or 40 mg as one dose **IM:** 40-60 mg as a single dose	G	4 mg
Dexamethasone (Dexamethasone Intensol®)	**Oral, IM, IV:** 0.25-0.75 mg PO once daily, 2 mg every 6 hours, 4 mg every 12 hours	G	0.75 mg
Betamethasone (Celestone Soluspan®)	**IM:** 0.25-9 mg/day	G	0.6 mg

* M= mineralocorticoid activity, G= glucocorticoid activity

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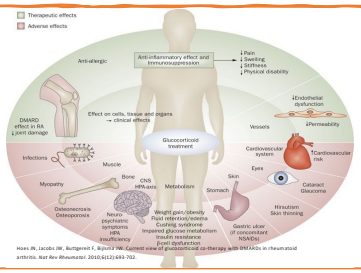
Relative Activities of Corticosteroids

Compound	Glucocorticoid activity	Mineralocorticoid activity
Natural steroids		
Cortisol	1	1
Corticosterone	0.3	15
Aldosterone	0.3	3,000
Deoxycorticosterone	0.2	100
Synthetic steroids		
Cortisone	0.8	0.8
Fludrocortisone	10	125
Prednisone	4	0.8
Prednisolone	4	0.8
Methylprednisolone	5	0.5
Betamethasone	25	0
Dexamethasone	25	0

Glucocorticoid and mineralocorticoid activity of natural and synthetic steroids, relative to cortisol.

13

Major Effects of Corticosteroids



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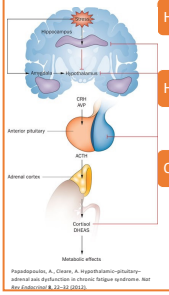
14

Endocrine System



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Hypothalamic-Pituitary-Adrenal Axis Suppression

- Adrenal Crisis

Hyperglycemia

- Augmentation of hepatic gluconeogenesis
- Inhibition of glucose uptake in adipose tissue

Other Effects

- Inhibition of growth hormone secretion
- Depression of thyroid-stimulating hormone
- Potentiation of catecholamine effects and stimulation of epinephrine synthesis

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McKay LI. *Consult Medicine*. 6th edition. 2003.

15

Knowledge Check

Long-term use of corticosteroids can lead to metabolic changes in the body. Which of the following statements accurately describe the mechanism by which corticosteroids contribute to these changes?

A) Corticosteroids enhance insulin sensitivity
B) They promote gluconeogenesis and decrease glucose uptake in peripheral tissue
C) Corticosteroids increase the secretion of thyroid hormones
D) They stimulate the production of adiponectin

16

Knowledge Check

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A) Corticosteroids enhance insulin sensitivity
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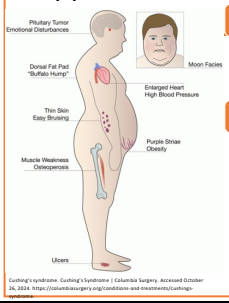
17

Appearance



Cushingoid features

- Redistribution of body fat with truncal obesity
- Buffalo hump
- Moon face

Weight gain

Increased appetite → Increase in food intake → Weight gain

Gastropathy or peptic ulcer disease

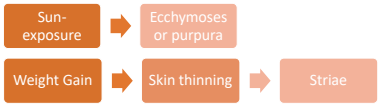
Cushing's syndrome. Cushing's Syndrome | Columbia Surgery. Accessed October 16, 2024. https://columbiasurgery.org/conditions-and-treatments/cushings-syndrome

Boumpas DT. *Ann Intern Med*. 1993.
Hoscher D. *Ann Rheum Dis*. 2009.

18

Dermatologic Effects

- Skin thinning, striae, and ecchymoses



- Acne
- Hirsutism
- Patients may benefit from photoprotective measures and keeping the skin moisturized.

Fardet L, et al. Br J Dermatol. 2007.

19

Knowledge Check

Which of the following is a common long-term side effect of corticosteroid use?

A) Reduced hair growth
B) Weight gain
C) Improved skin elasticity
D) Decreased appetite

20

Knowledge Check

Which of the following is a common long-term side effect of corticosteroid use?

A) Reduced hair growth
B) Weight gain
C) Improved skin elasticity
D) Decreased appetite

21

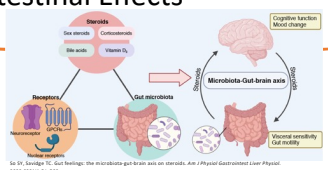
Cardiovascular Effects

Fluid retention	Hypertension	Hyperlipidemia
Premature atherosclerotic disease	Arrhythmias	Pulmonary emboli and venous thrombotic events

Wei L, et al. *Ann Intern Med.* 2004.

22

Gastrointestinal Effects



So SY, Savidge TC. Gut feelings: the microbiota-gut-brain axis on steroids. *Am J Physiol Gastrointest Liver Physiol.* 2022;322(1):G1-G20.

Upper gastrointestinal tract complications	Lower gastrointestinal tract complications
• Gastritis • Ulcer formation • Gastrointestinal bleeding	• Visceral perforation • Perforated sigmoid diverticular abscess

Stercioff S, et. al. *Surgery.* 1974.
Maeda S, et. al. *Ann Rheum Dis.* 2004.

23

Gastrointestinal Prophylactic Considerations

- Those on high doses of corticosteroids (Prednisone ≥ 20 mg/day) may benefit from acid suppressive therapy.
- Proton Pump Inhibitors
  - Ex: Pantoprazole (Protonix®) IV/DR 40 mg once daily
- Histamine Type 2 Receptor Antagonists
  - Ex: Famotidine (Pepcid®) 20 mg PO/IV once to twice daily

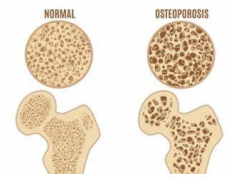
Fekheri RL. Corticosteroids and prophylaxis. *Clinical Correlations.* 2013.

24

Bone Effects

Osteoporosis
- Increase in bone resorption
- Suppression of bone formation
- Clinical manifestation: fractures

Osteonecrosis



This Photo by Unknown Author is licensed under CC BY

Cassalia E, et. al. *Osteoporos Int.* 2007.
Manologas SC, et. al. *Bone Miner Res.* 1996.

25

Osteoporosis Prophylactic Considerations

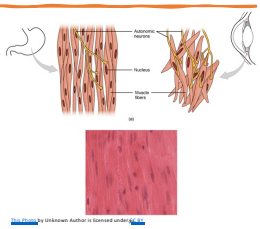
Initial Screening	Baseline dual-energy X-ray absorptiometry (DEXA)
Calcium Supplementation	All patients should be given 1,200-1,500mg of calcium per day
Vitamin D Supplementation	800IU-1,000IU of vitamin D per day, or enough to achieve a therapeutic level of 25-hydroxyvitamin D.
Bisphosphonate	Very high-risk groups should be started on a bisphosphonate

Fekheri RL. Corticosteroids and prophylaxis. *Clinical Correlations.* 2013.

26

Muscle Effects

- Myopathy
  - Acute
    - Generalized muscle atrophy
    - Rhabdomyolysis
  - Chronic
    - Symmetrical muscle weakness
- Prevention strategies:
  - Physical activity
- Treatment:
  - Gradual reduction steroid dose

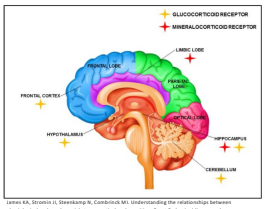


This Photo by Unknown Author is licensed under CC BY

Konagaya M, et. al. *Endocrinology.* 1986.

27

Neuropsychiatric Effects



James KA, Stronks JI, Steenkamp N, Combrinck MI. Understanding the relationships between physiological and psychosocial stress, cortisol and cognition. *Front Endocrinol (Lausanne).* 2023;14:1085950.

- Sleep disturbances
- Mood disorders
  - Mild euphoria
  - Anxiety
  - Hypomanic reactions and activated states
  - Depression
- Psychosis
  - "Steroid-induced psychosis"
- Memory impairment
  - "Steroid dementia"

Fardet L, et al. *Br J Dermatol.* 2007.

28

Knowledge Check

What is a potential psychological side effect of long-term corticosteroid use?

A) Decreased stress levels
B) Increased depression
C) Enhanced memory
D) Improved mood

29

Knowledge Check

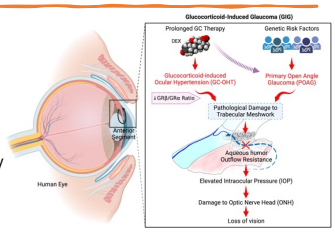
What is a potential psychological side effect of long-term corticosteroid use?

A) Decreased stress levels
B) Increased depression
C) Enhanced memory
D) Improved mood

30

Ophthalmologic Effects

- Cataracts
- Increased intraocular pressure
- Extremely rare complications
  - Exophthalmos
  - Central serous chorioretinopathy

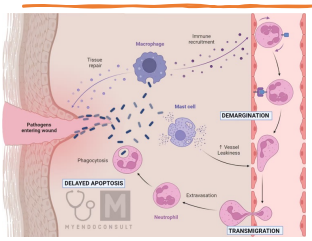


Patel PD, Kodati B, Clark AF. Role of Glucocorticoids and Glucocorticoid Receptors in Glaucoma Pathogenesis. Cells. 2023;12(20):2452.

Fardet L, et al. Br J Dermatol. 2007.

31

Hematologic Effects



- Glucocorticoids increase the release of neutrophils and granulocytes from bone marrow
- The increase in neutrophils often result in an increase white blood cell count

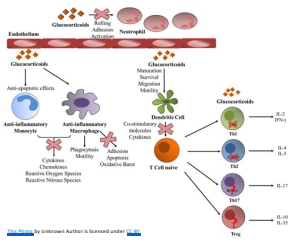
This Photo by Unknown Author is licensed under CC BY

Fardet L, et al. Br J Dermatol. 2007.

32

Immune System Effects

- The inhibition of inflammatory mediators can result in the suppression of immune system.
- Immunosuppression from steroids occurs when using more than 2 mg/kg/day or more than 20 mg/day of prednisone or prednisolone equivalent for more than 4 weeks.



This Photo by Unknown Author is licensed under CC BY

Fardet L, et al. Br J Dermatol. 2007.

33

Immune System Effects

- Risk factors associated with increased risk for infection

Patient-Related Factors	Therapy- and Disease-Related Factors
Older age (>65 years old)	Combination immunosuppressive therapy
Poor functional status	Long-term/maintenance immunosuppressive therapy to maintain response
Preexisting comorbidities	Polypharmacy
Socioeconomic status	Higher doses to achieve disease response

Malpica L, et al. *Hematology Am Soc Hematol Educ Program.* 2020.

34

Infection Prophylactic Considerations

- Screening and antimicrobial prophylaxis against tuberculosis, hepatitis B, *Strongyloides stercoralis*, and *Pneumocystis jirovecii pneumonia (PCP)* might be indicated in patients who are scheduled to be on high-dose corticosteroids for >4 weeks

Pneumocystis jirovecii pneumonia (PCP)	Trimethoprim/Sulfamethoxazole (TMP/SMX) (Bactrim®) 1 single-strength tablet (80mg/400mg) daily, or 1 double-strength tablet 3 times weekly.	Alternative therapies include: atovaquone (Mepron®), dapsone, nebulized pentamidine (Nebupent®)
Herpes Zoster (shingles)	Immunization indicated in all adults aged ≥ 50 years	Consider antiviral prophylaxis with acyclovir (Zovirax®) 400 mg daily

Malpica L, et al. *Hematology Am Soc Hematol Educ Program.* 2020.

35

Infection Prophylactic Considerations

Tuberculosis Reactivation	TB screening testing using tuberculin skin test or interferon-γ release assays	If positive test, refer to an infectious disease specialist
Strongyloides stercoralis (SS)	SS screening testing with stool sample for ova and parasites and serum IgG against SS	Prophylactic therapy with ivermectin (Stromectol®)for those at high-risk for severe strongyloidiasis
Hepatitis B Virus (HBV) Reactivation	HBV screening testing with anti-HBc and HBsAg	High-risk patient require antiviral prophylaxis with entecavir or tenofovir while moderate-risk patients can be monitored with serial HBV DNA monitoring

Malpica L, et al. *Hematology Am Soc Hematol Educ Program.* 2020.

36

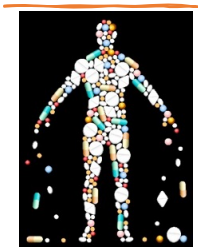
Short-Term Versus Long-Term Effects

Short-term glucocorticosteroid therapy	Long-term glucocorticosteroid therapy	
Gastrointestinal intolerance	**Musculoskeletal**	**Metabolic**
Increased predisposition to infections	Growth retardation	Hyperglycemia
Delayed wound healing	Osteoporosis	Truncal obesity
Increased appetite Hyperglycemia	Myopathy	Hyperlipidemia
Fluid and sodium retention	Avascular necrosis of bone	Hypokalemia
Mood changes	**HPA axis**	Hypocalcemia
Weakness	Suppression	**Cutaneous**
Insomnia	Withdrawal syndrome	Hirsutism
Amenorrhea	Adrenal crisis	Atrophy
Acne	**Ophthalmologic**	Hyperpigmentation
	Cataracts	Acne
	Glaucoma	**Nervous system**
	Gastrointestinal	Mood and personality changes
	Gastritis	Psychosis
	Peptic ulcer disease	Pseudotumor cerebri
	Pancreatitis	
	Intestinal perforation	

Aulakh R, Singh S., *Indian J Pediatr.* 2008.

37

General Treatment Consideration



Utilize the lowest dose of glucocorticoids for the shortest period of time

Preventative interventions

Monitor patients for adverse effects and pursue corrective interventions when possible

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Patient Education and Management

- What is this drug used for?
  - It is used for many health problems like allergies, asthma, adrenal gland problems, blood problems, skin rashes, and many more.
- Steroid Administration Recommendations:
  - Take with food to avoid stomach upset.
  - Take in the morning to avoid sleep disturbances.
- General Recommendations:
  - Adhere to their age-based immunization schedule.
  - Live vaccines are contraindicated in patients receiving immunosuppressive therapy

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Patient Education and Management

- Potential Side Effects

Side Effects	What to do
Skin: thinned skin, easy bruising, slow wound healing	Avoid trauma and sun exposure. Keep skin clean, dry, and moisturize
Gastrointestinal: stomach irritation, stimulated appetite	Avoid NSAIDs and report stomach pain, heartburn, and black/tarry stools
Musculoskeletal: achiness, muscle weakness, osteoporosis	Physical activity to maintain strength, report bone pain, optimize vitamin D/calcium
Cardiovascular: high blood pressure, swelling	Incorporate a low sodium diet
Endocrine: increased blood sugar, adrenal gland insufficiency	Do not stop steroids abruptly without informing a medical professional
Psychological: personality changes, depression, anxiety, insomnia	Report to medical teams and include caregiver in discussion
Eyes: blurred vision, cataracts	See optometrist for worsening blurred vision
Immune system: may increase risk for infections	Avoid contact with ill people

40

Indications for Withdrawing Corticosteroids

- Maximum desired therapeutic benefit
- Inadequate therapeutic benefit
- Serious side effects
- Unresponsive steroid-induced acute psychosis

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Steroid Tapering

Short-term glucocorticoid therapy (< 2 weeks)	Stop without tapering
> 40 mg/day of prednisone or equivalent	5-10 mg/day every 1-2 weeks
Prednisone doses 20-40 mg/day	5 mg/day every 1-2 weeks
Prednisone doses 10-20 mg/day	2.5 mg/day every 2-3 weeks
Prednisone doses 5-10 mg/day	1 mg/day every 2-4 weeks
Prednisone doses <5 mg/day	0.5 mg/day

Brett AS. *New England Journal of Medicine*. 2024.

42

Abrupt Steroid Withdrawal

- Symptoms and signs of steroid withdrawal syndrome
  - High fever
  - Anorexia
  - Nausea
  - Lethargy
  - Malaise
  - Other: abdominal pain, vomiting, postural hypotension, hyponatremia, and hyperkalemia
  - Arthralgias
  - Desquamation of the skin
  - Weakness
  - Weight loss

Margolin L, Cope DK, Bakst-Sisser R, Greenspan J. *J Pain Symptom Manage*. 2007.

43

Abrupt Steroid Withdrawal

- Possible etiologies of steroid withdrawal syndrome
  - Adrenal insufficiency
  - Adapted tissue requirement for adrenocortical steroids
  - Increased interleukin-6 and tumor necrosis factor α and interleukin-1β
- Treatment
  - Prevention of steroid withdrawal syndrome
  - Fever workup
  - Reinstitution of steroids
  - Taper steroids

Margolin L, Cope DK, Bakst-Sisser R, Greenspan J. *J Pain Symptom Manage*. 2007.

44

Back to the Case Report

DADE COUNTY PHARMACY ASSOCIATION
29 Years Featuring
South Florida Pharmacy Residents

45

Case Report

- A 55-year-old female patient was admitted to the general medicine department with complaints of facial puffiness for one year, neck pain for three days, giddiness, headache, eye pain, exertional dyspnea, generalized weakness, and decreased sleep.
- **Past Medical History**: Hypothyroidism, hypertension, right knee pain
- **Home Medications:** levothyroxine 25mcg , telmisartan/hydrochlorothiazide 40mg/2.5mg, dexamethasone 0.5 mg
- **Physical Examination**: facial puffiness +ve, buffalo hump , B/L pitting type of edema
- **Imaging:** Ultrasound Abdomen showed fatty changes in liver and hepatomegaly

Poludasari SK, Sridevi CH. *Journal of Drug Delivery and Therapeutics*. 2022.

46

Case Report

Parameter	Value
Random blood glucose	270 mg/dL (H)
Fasting blood glucose	166 mg/dL (H)
HbA1c	7.4% (H)
Total cholesterol	305 mg/dL (H)
High-Density Lipoprotein	59 mg/dL (L)
Low-Density Lipoprotein	179 mg/dL (H)
Very Low-Density Lipoprotein	6.6 mg/dL
Triglycerides	277 mg/dL (H)
25-Hydroxy Vit D test	13.69 ng/mL (L)

Poludasari SK, Sridevi CH. *Journal of Drug Delivery and Therapeutics*. 2022.

47

Case Report

System	Side Effect
Endocrine	Hypothyroidism
Appearance	Face puffiness, buffalo hump
Cardiovascular	Hypertension, fluid retention, hyperlipidemia
Gastrointestinal	Hepatomegaly
Skeletal	Vitamin D and calcium deficiency
Muscular	Generalized weakness
Neurologic	Decreased sleep
Ophthalmologic	Eye pain

Poludasari SK, Sridevi CH. *Journal of Drug Delivery and Therapeutics*. 2022.

48

Knowledge Check

SY, a 52 YO female, presents to the clinic with complaints of severe mood swings, weight gain, and worsening diabetes control. She reports that these symptoms began approximately two weeks after her physician prescribed a course of oral corticosteroids for an acute exacerbation.

PMH: asthma, HTN, T2DM

Home medications: Prednisone 40 mg QD x 10 days (started 14 days ago for asthma exacerbation), Metformin 500 mg BID, albuterol

What side effect(s) of corticosteroids is SY experiencing?

A. Weight Gain
B. Hyperglycemia
C. Mood Swings
D. All the Above

49

Knowledge Check

SY, a 52 YO female, presents to the clinic with complaints of severe mood swings, weight gain, and worsening diabetes control. She reports that these symptoms began approximately two weeks after her physician prescribed a course of oral corticosteroids for an acute exacerbation.

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50

References

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4. McMahon M, Gerich J, Rizza R. Effects of glucocorticoids on carbohydrate metabolism. *Diabetes Metab Rev*. 1988;4(1):17-30.
5. Fardet L, Flahault A, Kettaneh A, et al. Corticosteroid-induced clinical adverse events: frequency, risk factors and patient's opinion. *Br J Dermatol*. 2007;157(1):142-148. Wei L, MacDonald TM, Walker BR. Taking glucocorticoids by prescription is associated with subsequent cardiovascular disease. *Ann Intern Med*. 2004;141(10):764-770.
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8. Manolagas SC, Weinstein RS. New developments in the pathogenesis and treatment of steroid-induced osteoporosis. *J Bone Miner Res*. 1999;14(7):1061-1066.
9. Schäcke H, Döcke WD, Asadullah K. Mechanisms involved in the side effects of glucocorticoids. *Pharmacol Ther*. 2002;96(1):23-43.
10. Konagaya M, Bernard PA, Max SR. Blockade of glucocorticoid receptor binding and inhibition of dexamethasone-induced muscle atrophy in the rat by RU38486, a potent glucocorticoid antagonist. *Endocrinology*. 1986;119(1):375-380.
11. McKay LI, Cidlowski JA. Physiologic and Pharmacologic Effects of Corticosteroids. In: Kufe DW, Pollock RE, Weichselbaum RR, et al., editors. Holland-Frei Cancer Medicine. 6th edition. Hamilton (ON): BC Decker; 2003.
12. Aulakh R, Singh S. Strategies for minimizing corticosteroid toxicity: a review. *Indian J Pediatr*. 2008.
13. Poludasari SK, Sridevi CH. A Case Report on Multiple Adverse Events Associated with Systemic Usage of Dexamethasone. *Journal of Drug Delivery and Therapeutics*. 2022
14. Malpica L, Moll S. Practical approach to monitoring and prevention of infectious complications associated with systemic corticosteroids. *Hematology Am Soc Hematol Educ Program*. 2020;2020(1):319-327.
15. Margolin L, Cope DK, Bakst-Sisser R, Greenspan J. The steroid withdrawal syndrome: a review of the implications, etiology, and treatments. *J Pain Symptom Manage*. 2007;33(2):224-228.

51

Thank you!
Any questions?

52

What's the Skinny:
Long-Term Health Effects of GLP1 and GIP Use

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Miami, FL
01/26/2025

1

1

Disclosure

All authors of this presentation have nothing to disclose concerning possible financial or personal relationships with commercial entities that may have direct or indirect interest in the subject matter of this presentation.

2

2

Objectives

- Explain the **mechanism of action** by which glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) medications exert their effects
- Recognize **potential risks, side effects, and long-term health benefits** associated with the prolonged use of GLP-1 and GIP medications
- Analyze current **clinical evidence** and explore future research directions for GLP-1 and GIP use

3

3

Introduction

- GLP-1 and GIP are part of the hormonal peptides knowns as **incretins** produced in the gastrointestinal tract

4

Introduction

- GLP-1 and GIP are part of the hormonal peptides knowns as **incretins** produced in the gastrointestinal tract
- Combined, they form the **incretin effect**
  - First proposed in the 1970s and centered around the idea that **insulin secretion seemed to be higher** after oral glucose intake than after intravenous glucose administration

5

Introduction

- GLP-1 and GIP are part of the hormonal peptides knowns as **incretins** produced in the gastrointestinal tract
- Combined, they form the **incretin effect**
  - First proposed in the 1970s and centered around the idea that **insulin secretion seemed to be higher** after oral glucose intake than after intravenous glucose administration
- Approximately 50-70% of the postprandial insulin responses can be attributed to the incretin effect, which is **reduced in people with type 2 diabetes mellitus**

6

Mechanism of Action

GLP-1 is a 30 amino acid peptide produced in the **distal ileum and colon** by enteroendocrine L cells

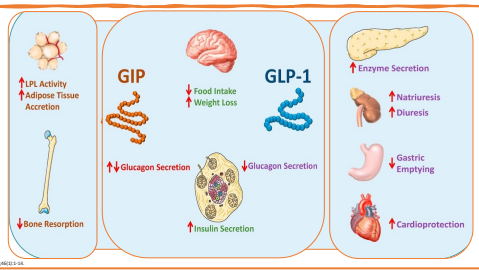
GIP is a 42 amino acid peptide produced in the **duodenum and jejunum** by enteroendocrine K cells

Both hormones are released after ingestion, stimulating pancreatic β cells and increasing insulin production in a glucose-dependent manner

7 Cardiovascular Diabetology. 2021;20(1):1-5.

7

Mechanism of Action



8 Molecular Metabolism. 2021;46(C):1-14.

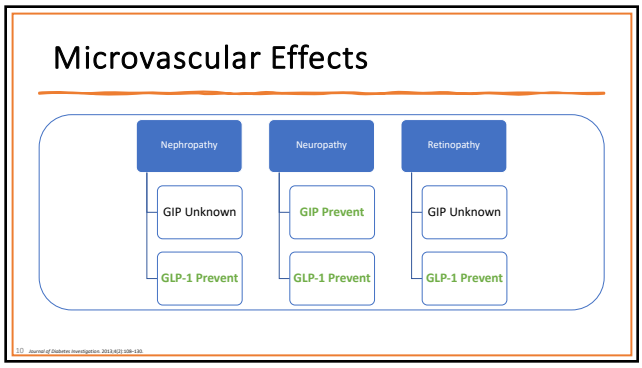
8

Macrovascular Effects

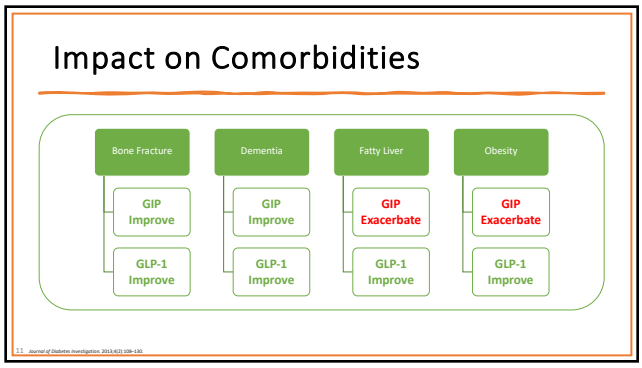
Cardiovascular disease	Cerebrovascular disease	Dyslipidemia	Hypertension	Inflammation	Peripheral artery disease
GIP Unknown	GIP Unknown	GIP Unknown	GIP Unknown	GIP Prevent	GIP Unknown
GLP-1 Prevent	GLP-1 Prevent	GLP-1 Prevent	GLP-1 Prevent	GLP-1 Prevent	GLP-1 Prevent

9 Journal of Diabetes Investigation. 2013;4(2):108-130.

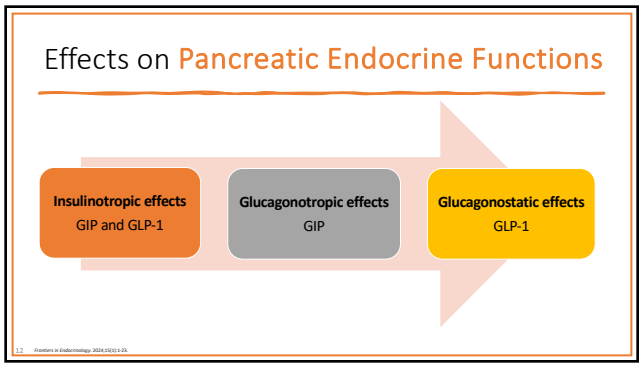
9


Microvascular Effects
Nephropathy
Neuropathy
Retinopathy
GIP Unknown
GIP Prevent
GIP Unknown
GLP-1 Prevent
GLP-1 Prevent
GLP-1 Prevent

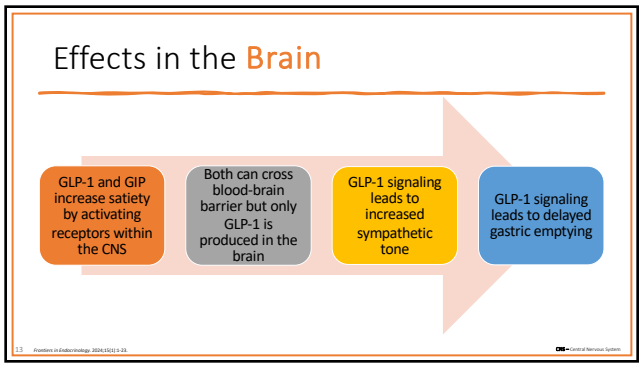
10


Impact on Comorbidities
Bone Fracture
Dementia
Fatty Liver
Obesity
GIP Improve
GIP Improve
GIP Exacerbate
GIP Exacerbate
GLP-1 Improve
GLP-1 Improve
GLP-1 Improve
GLP-1 Improve

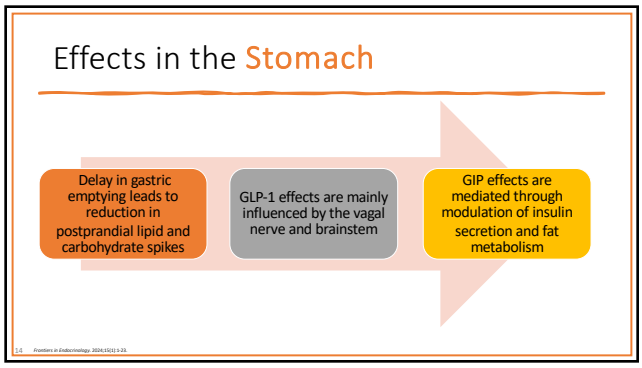
11


Effects on Pancreatic Endocrine Functions
Insulinotropic effects
GIP and GLP-1
Glucagonotropic effects
GIP
Glucagonostatic effects
GLP-1

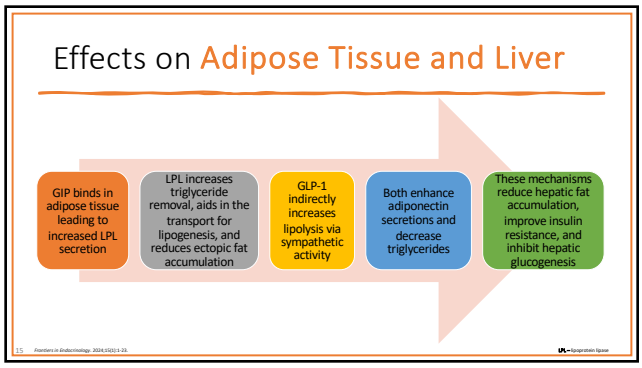
12


Effects in the Brain
GLP-1 and GIP increase satiety by activating receptors within the CNS
Both can cross blood-brain barrier but only GLP-1 is produced in the brain
GLP-1 signaling leads to increased sympathetic tone
GLP-1 signaling leads to delayed gastric emptying

13


Effects in the Stomach
Delay in gastric emptying leads to reduction in postprandial lipid and carbohydrate spikes
GLP-1 effects are mainly influenced by the vagal nerve and brainstem
GIP effects are mediated through modulation of insulin secretion and fat metabolism

14


Effects on Adipose Tissue and Liver
GIP binds in adipose tissue leading to increased LPL secretion
LPL increases triglyceride removal, aids in the transport for lipogenesis, and reduces ectopic fat accumulation
GLP-1 indirectly increases lipolysis via sympathetic activity
Both enhance adiponectin secretions and decrease triglycerides
These mechanisms reduce hepatic fat accumulation, improve insulin resistance, and inhibit hepatic glucogenesis

15

Knowledge Check

What is the main mechanism by which GLP-1 and GIP medications contribute to the management of type 2 diabetes?

A. Increase glucose absorption in the intestines, leading to improved postprandial glucose control
B. Enhance insulin secretion in a glucose-dependent manner and reduce appetite, thereby improving glycemic control
C. Stimulate the liver to increase glycogen storage and inhibit fat breakdown, which helps manage blood sugar levels
D. Serve as replacement hormones for insulin, eliminating the need for exogenous insulin in all patients

16

16

Knowledge Check

What is the main mechanism by which GLP-1 and GIP medications contribute to the management of type 2 diabetes?

A. Increase glucose absorption in the intestines, leading to improved postprandial glucose control
B. Enhance insulin secretion in a glucose-dependent manner and reduce appetite, thereby improving glycemic control
C. Stimulate the liver to increase glycogen storage and inhibit fat breakdown, which helps manage blood sugar levels
D. Serve as replacement hormones for insulin, eliminating the need for exogenous insulin in all patients

17

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Available Agents & Indications

18

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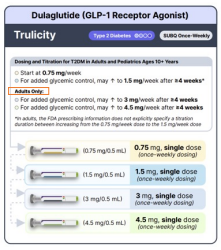
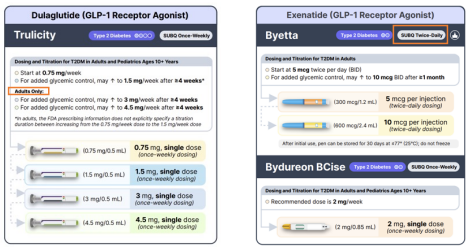
Available Agents & Indications



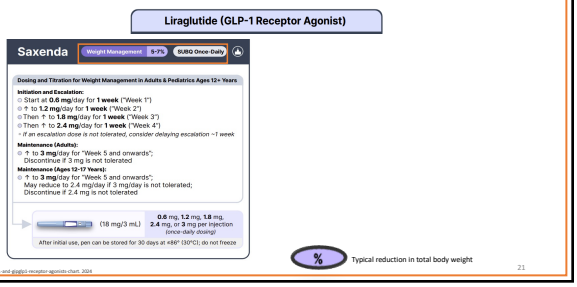
19

Available Agents & Indications

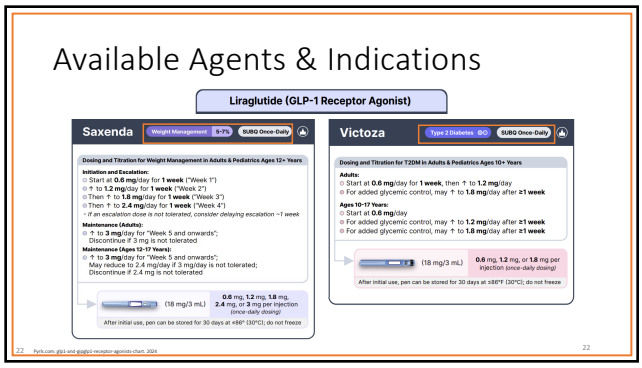


20

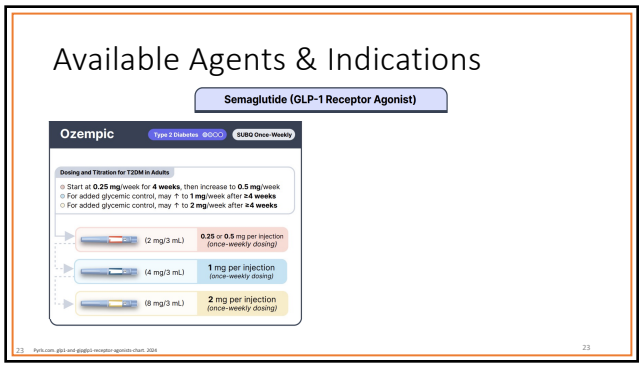
Available Agents & Indications



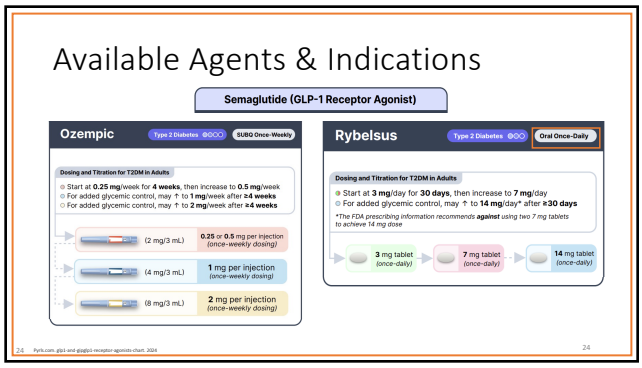
21


Available Agents & Indications
Liraglutide (GLP-1 Receptor Agonist)
Saxenda
Weight Management
5-7%
SUBQ Once-Daily
Dosing and Titration for Weight Management in Adults & Pediatrics Ages 12+ Years
Initiation and Escalation:
Start at 0.6 mg/day for 1 week ("Week 1")
↑ to 1.2 mg/day for 1 week ("Week 2")
Then ↑ to 1.8 mg/day for 1 week ("Week 3")
Then ↑ to 2.4 mg/day for 1 week ("Week 4")
~ If an escalation dose is not tolerated, consider delaying escalation ~1 week
Maintenance (Adults):
↑ to 3 mg/day for "Week 5 and onwards";
Discontinue if 3 mg is not tolerated
Maintenance (Ages 12-17 Years):
↑ to 3 mg/day for "Week 5 and onwards";
May reduce to 2.4 mg/day if 3 mg/day is not tolerated;
Discontinue if 2.4 mg is not tolerated
(18 mg/3 mL)
0.6 mg, 1.2 mg, 1.8 mg, 2.4 mg, or 3 mg per injection (once-daily dosing)
After initial use, pen can be stored for 30 days at ≤86° (30°C); do not freeze
Victoza
Type 2 Diabetes
SUBQ Once-Daily
Dosing and Titration for T2DM in Adults & Pediatrics Ages 10+ Years
Adults:
Start at 0.6 mg/day for 1 week, then ↑ to 1.2 mg/day
For added glycemic control, may ↑ to 1.8 mg/day after ≥1 week
Ages 10-17 Years:
Start at 0.6 mg/day
For added glycemic control, may ↑ to 1.2 mg/day after ≥1 week
For added glycemic control, may ↑ to 1.8 mg/day after ≥1 week
(18 mg/3 mL)
0.6 mg, 1.2 mg, or 1.8 mg per injection (once-daily dosing)
After initial use, pen can be stored for 30 days at ≤86°F (30°C); do not freeze
22
Pyrls.com_glp1-and-glp/glp1-receptor-agonists-chart_2024
22

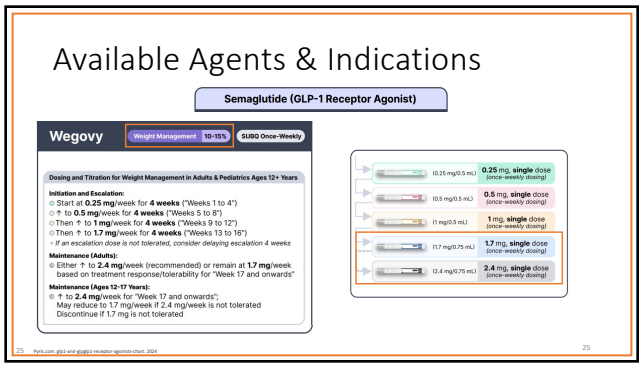
22


Available Agents & Indications
Semaglutide (GLP-1 Receptor Agonist)
Ozempic
Type 2 Diabetes
SUBQ Once-Weekly
Dosing and Titration for T2DM in Adults
Start at 0.25 mg/week for 4 weeks, then increase to 0.5 mg/week
For added glycemic control, may ↑ to 1 mg/week after ≥4 weeks
For added glycemic control, may ↑ to 2 mg/week after ≥4 weeks
(2 mg/3 mL)
0.25 or 0.5 mg per injection (once-weekly dosing)
(4 mg/3 mL)
1 mg per injection (once-weekly dosing)
(8 mg/3 mL)
2 mg per injection (once-weekly dosing)
23
Pyrls.com_glp1-and-glp/glp1-receptor-agonists-chart_2024
23

23


Available Agents & Indications
Semaglutide (GLP-1 Receptor Agonist)
Ozempic
Type 2 Diabetes
SUBQ Once-Weekly
Dosing and Titration for T2DM in Adults
Start at 0.25 mg/week for 4 weeks, then increase to 0.5 mg/week
For added glycemic control, may ↑ to 1 mg/week after ≥4 weeks
For added glycemic control, may ↑ to 2 mg/week after ≥4 weeks
(2 mg/3 mL)
0.25 or 0.5 mg per injection (once-weekly dosing)
(4 mg/3 mL)
1 mg per injection (once-weekly dosing)
(8 mg/3 mL)
2 mg per injection (once-weekly dosing)
Rybelsus
Type 2 Diabetes
Oral Once-Daily
Dosing and Titration for T2DM in Adults
Start at 3 mg/day for 30 days, then increase to 7 mg/day
For added glycemic control, may ↑ to 14 mg/day* after ≥30 days
*The FDA prescribing information recommends against using two 7 mg tablets to achieve 14 mg dose
3 mg tablet (once-daily)
7 mg tablet (once-daily)
14 mg tablet (once-daily)
24
Pyrls.com_glp1-and-glp/glp1-receptor-agonists-chart_2024
24

24


Available Agents & Indications
Semaglutide (GLP-1 Receptor Agonist)
Wegovy
Weight Management 10-15%
SUBQ Once-Weekly
Dosing and Titration for Weight Management in Adults & Pediatrics Ages 12+ Years
Initiation and Escalation:
Start at 0.25 mg/week for 4 weeks ("Weeks 1 to 4")
↑ to 0.5 mg/week for 4 weeks ("Weeks 5 to 8")
Then ↑ to 1 mg/week for 4 weeks ("Weeks 9 to 12")
Then ↑ to 1.7 mg/week for 4 weeks ("Weeks 13 to 16")
If an escalation dose is not tolerated, consider delaying escalation 4 weeks
Maintenance (Adults):
Either ↑ to 2.4 mg/week (recommended) or remain at 1.7 mg/week based on treatment response/tolerability for "Week 17 and onwards"
Maintenance (Ages 12-17 Years):
↑ to 2.4 mg/week for "Week 17 and onwards";
May reduce to 1.7 mg/week if 2.4 mg/week is not tolerated
Discontinue if 1.7 mg is not tolerated
(0.25 mg/0.5 mL) 0.25 mg, single dose (once-weekly dosing)
(0.5 mg/0.5 mL) 0.5 mg, single dose (once-weekly dosing)
(1 mg/0.5 mL) 1 mg, single dose (once-weekly dosing)
(1.7 mg/0.75 mL) 1.7 mg, single dose (once-weekly dosing)
(2.4 mg/0.75 mL) 2.4 mg, single dose (once-weekly dosing)
25
25

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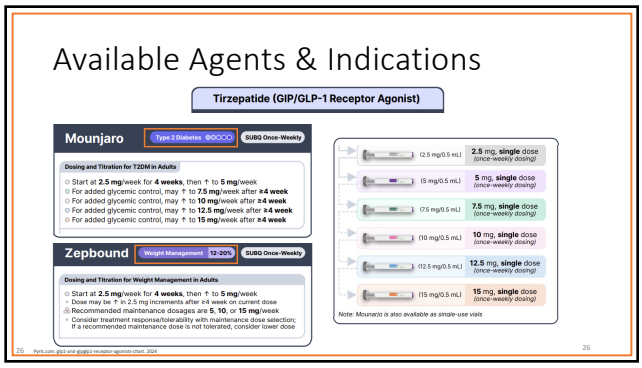
Available Agents & Indications
Tirzepatide (GIP/GLP-1 Receptor Agonist)
Mounjaro
Type 2 Diabetes
SUBQ Once-Weekly
Dosing and Titration for T2DM in Adults
Start at 2.5 mg/week for 4 weeks, then ↑ to 5 mg/week
For added glycemic control, may ↑ to 7.5 mg/week after ≥4 week
For added glycemic control, may ↑ to 10 mg/week after ≥4 week
For added glycemic control, may ↑ to 12.5 mg/week after ≥4 week
For added glycemic control, may ↑ to 15 mg/week after ≥4 week
Zepbound
Weight Management 12-20%
SUBQ Once-Weekly
Dosing and Titration for Weight Management in Adults
Start at 2.5 mg/week for 4 weeks, then ↑ to 5 mg/week
Dose may be ↑ in 2.5 mg increments after ≥4 week on current dose
Recommended maintenance dosages are 5, 10, or 15 mg/week
Consider treatment response/tolerability with maintenance dose selection; If a recommended maintenance dose is not tolerated, consider lower dose
(2.5 mg/0.5 mL) 2.5 mg, single dose (once-weekly dosing)
(5 mg/0.5 mL) 5 mg, single dose (once-weekly dosing)
(7.5 mg/0.5 mL) 7.5 mg, single dose (once-weekly dosing)
(10 mg/0.5 mL) 10 mg, single dose (once-weekly dosing)
(12.5 mg/0.5 mL) 12.5 mg, single dose (once-weekly dosing)
(15 mg/0.5 mL) 15 mg, single dose (once-weekly dosing)
Note: Mounjaro is also available as single-use vials
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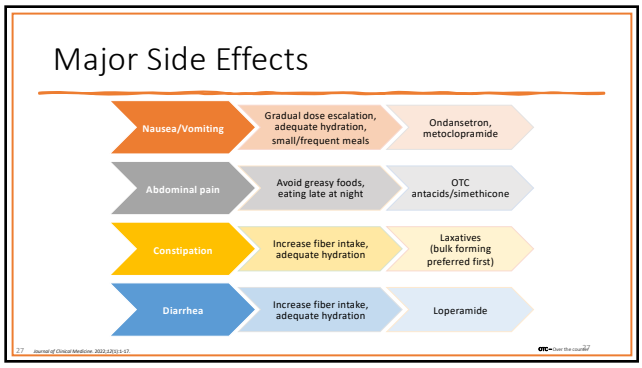
Major Side Effects
Nausea/Vomiting
Gradual dose escalation, adequate hydration, small/frequent meals
Ondansetron, metoclopramide
Abdominal pain
Avoid greasy foods, eating late at night
OTC antacids/simethicone
Constipation
Increase fiber intake, adequate hydration
Laxatives (bulk forming preferred first)
Diarrhea
Increase fiber intake, adequate hydration
Loperamide
OTC=Over the counter
27
27

27

Counseling Points

Administration	Injection technique	Site and rotation Possible reactions
Hypoglycemia Risk	Indication diabetes vs. weight loss	Combination with other agents
Missed Dose	Timing before next dose	Only using as prescribed
Lifestyle Modifications	Diet/exercise	Consistency is key

28 Ozempic [prescribing information]. Plainsboro, NJ: Novo Nordisk Inc.; 2017. 28

28

Additional Remarks

- Patients may experience more/less side effects depending on **injection site and administration time**
  - **Abdomen** is the preferred **injection site** due to consistent absorption rate, but the **thigh** or **upper arm** can be used
- Side effects can be experienced at **any point** while receiving treatment
  - Side effects can be more severe at **initiation** and with **dose escalations**

29 Ozempic [prescribing information]. Plainsboro, NJ: Novo Nordisk Inc.; 2017. 29

29

Long-Term Health Effects – The Bad

30 30

30

Long-Term Health Effects – The Bad

- **Gastroparesis:** Can exacerbate or worsen symptoms of gastroparesis

31

Long-Term Health Effects – The Bad

- **Gastroparesis:** Can exacerbate or worsen symptoms of gastroparesis
  - **Risk of aspiration** is elevated during surgical procedures due to the effects of delayed gastric emptying
  - **Discontinue** prior to gastric emptying tests to ensure accurate evaluation for gastroparesis

32

Long-Term Health Effects – The Bad

- **Gastroparesis:** Can exacerbate or worsen symptoms of gastroparesis
  - **Risk of aspiration** is elevated during surgical procedures due to the effects of delayed gastric emptying
  - **Discontinue** prior to gastric emptying tests to ensure accurate evaluation for gastroparesis

- Gastrointestinal side effects overall occur in up to **10–20% of patients but true prevalence of gastroparesis is unknown**
- Timing for discontinuation before anesthesia varies based on individual patient risk and type of surgery
  - General recommendations is to **stop at least 48–72 hours** before anesthesia

33

Long-Term Health Effects – The Bad

- **Pancreatitis:** Stimulation of GLP-1/GIP receptors has potential to induce pancreatitis and increase the risk of pancreatic cancer

34

Long-Term Health Effects – The Bad

- **Pancreatitis:** Stimulation of GLP-1/GIP receptors has potential to induce pancreatitis and increase the risk of pancreatic cancer
  - The risk has been reported in **post-marketing studies**
  - No recent studies to assess potential increased risk in patients with a history of pancreatitis

35

Long-Term Health Effects – The Bad

- **Pancreatitis:** Stimulation of GLP-1/GIP receptors has potential to induce pancreatitis and increase the risk of pancreatic cancer
  - The risk has been reported in **post-marketing studies**
  - No recent studies to assess potential increased risk in patients with a history of pancreatitis

- Overall incidence rate **remains <0.2%** across most clinical trials
  - **SUSTAIN**: 0.1–0.2%
  - **STEP**: <0.1%
  - **SURPASS**: <0.1%

36

Long-Term Health Effects – The Bad

- **Thyroid Cancer:** Carcinogenicity studies suggest a dose- and time-dependent increased risk of medullary thyroid carcinomas

37 Diabetes Care. 2022;45(2):384–390. 37

37

Long-Term Health Effects – The Bad

- **Thyroid Cancer:** Carcinogenicity studies suggest a dose- and time-dependent increased risk of medullary thyroid carcinomas
  - **Elevated risk** of both, overall thyroid cancer and medullary thyroid cancer, with prolonged use
  - Risk and incidence is low but all agents have a **FDA Black Box Warning**

38 Diabetes Care. 2022;45(2):384–390. FDA—Federal Drug Administration 38

38

Long-Term Health Effects – The Bad

- **Thyroid Cancer:** Carcinogenicity studies suggest a dose- and time-dependent increased risk of medullary thyroid carcinomas
  - **Elevated risk** of both, overall thyroid cancer and medullary thyroid cancer, with prolonged use
  - Risk and incidence is low but all agents have a **FDA Black Box Warning**

- Incidence has been reported in **<0.1%** of patients
- Tumors have been observed in animal studies; however **human risk remains not well-established**
- Post-marketing data has not provided **definitive evidence** to confirm a substantial risk increase

39 Diabetes Care. 2022;45(2):384–390. FDA—Federal Drug Administration 39

39

Long-Term Health Effects – The Bad

- **Proliferative Retinopathy:** Sudden fluctuations in blood glucose, especially reductions, can increase retinal inflammation and oxidative stress

40

Long-Term Health Effects – The Bad

- **Proliferative Retinopathy:** Sudden fluctuations in blood glucose, especially reductions, can increase retinal inflammation and oxidative stress
  - Commonly seen in patients with **long-standing diabetes and poor baseline control**
  - Progression is **typically reversible** but underlying mechanisms remain poorly understood

41

Long-Term Health Effects – The Bad

- **Proliferative Retinopathy:** Sudden fluctuations in blood glucose, especially reductions, can increase retinal inflammation and oxidative stress
  - Commonly seen in patients with **long-standing diabetes and poor baseline control**
  - Progression is **typically reversible** but underlying mechanisms remain poorly understood

- The **SUSTAIN** trials reported **diabetic retinopathy complications**
- In 2023, the **FDA** issued a **warning for select GLP-1 receptor agonists** for the potential risk of **progression**, particularly in patients with a history of diabetic retinopathy or with rapidly improving glycemic control

42

Long-Term Health Effects – The Good

43

43

Long-Term Health Effects – The Good

- **Cardiovascular:** Significant cardiovascular benefits for adults, with or without diabetes, especially in reducing MACE, stroke, and MI

44 *Frontiers in Endocrinology.* 2024;15(1):1-16.

MACE – Major Adverse Cardiovascular Events
MI – Myocardial Infarction

44

Long-Term Health Effects – The Good

- **Cardiovascular:** Significant cardiovascular benefits for adults, with or without diabetes, especially in reducing MACE, stroke, and MI
  - Benefits may result from **direct effects**, including improved endothelial function, reduced inflammation, and cardiac metabolism modulation
  - **Indirect effects** are achieved through improved glycemic control, weight loss, and favorable changes in lipid profiles

45 *Frontiers in Endocrinology.* 2024;15(1):1-16.

MACE – Major Adverse Cardiovascular Events
MI – Myocardial Infarction

45

Long-Term Health Effects – The Good

- **Renal:** Reduction in albuminuria and may slow eGFR decline in individuals with T2DM

46

Long-Term Health Effects – The Good

- **Renal:** Reduction in albuminuria and may slow eGFR decline in individuals with T2DM
  - Benefits likely due to reduced renal inflammation, improved renal hemodynamics, and **direct effects** on proximal tubular cells
  - Ability to prevent progression to chronic kidney failure has not yet been established

47

Long-Term Health Effects – The Good

- **Weight Loss:** Highly effective weight loss in both the short- and long-term

48

Long-Term Health Effects – The Good

- **Weight Loss:** Highly effective weight loss in both the short- and long-term
  - Benefits result from appetite regulation, delayed gastric emptying, and improved insulin sensitivity, which reduce fat storage
  - GLP-1/GIP medications aid in initial weight loss and support long-term weight maintenance

JAMA. 2024;331(1):38–48.
Nature Medicine. 2022;28(10):2083–2091.

49

Long-Term Health Effects – The Good

- **Weight Loss:** Highly effective weight loss in both the short- and long-term
  - Benefits result from appetite regulation, delayed gastric emptying, and improved insulin sensitivity, which reduce fat storage
  - GLP-1/GIP medications aid in initial weight loss and support long-term weight maintenance

- STEP 5 trial showed weekly semaglutide was associated with **sustained weight loss of 15.2% at week 104**
- SURMOUNT-4 trial showed participants experienced a **mean weight reduction of 20.9%** in the 36-week lead-in period with tirzepatide
  - Participants who continued for an additional 52 weeks had an **extra 5.5% weight loss, with a mean of 25% loss from the initial baseline**

JAMA. 2024;331(1):38–48.
Nature Medicine. 2022;28(10):2083–2091.

50

Long-Term Health Effects – The Good

- **Metabolic Dysfunction-Associated Steatotic Liver Disease:** Anti-inflammatory effects are beneficial in prevention of progression of disease states like nonalcoholic steatohepatitis and cirrhosis

Lancet. 2016;387(10019):679–690.
The New England Journal of Medicine. 2021;384(12):1113–1124.

51

Long-Term Health Effects – The Good

- **Metabolic Dysfunction-Associated Steatotic Liver Disease:** Anti-inflammatory effects are beneficial in prevention of progression of disease states like nonalcoholic steatohepatitis and cirrhosis
  - Benefits are due to the improvement in metabolic control, reduction of fat content in the liver, and slowing of fibrosis progression
  - May also **promote liver regeneration** by improving the metabolic environment

Lancet. 2016;387(10019):679-690.
The New England Journal of Medicine. 2021;384(12):1113–1124.

52

52

Knowledge Check

Which of the following is a major side effect associated with the use of GLP-1 and GIP medications?

A. Increased risk of hypoglycemia, especially when used with metformin
B. Significant weight gain due to appetite changes
C. Gastrointestinal issues such as nausea, vomiting, and diarrhea
D. Elevated blood pressure and heart rate

53

53

Knowledge Check

Which of the following is a major side effect associated with the use of GLP-1 and GIP medications?

A. Increased risk of hypoglycemia, especially when used with metformin
B. Significant weight gain due to appetite changes
C. Gastrointestinal issues such as nausea, vomiting, and diarrhea
D. Elevated blood pressure and heart rate

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Clinical Evidence

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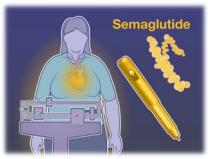
Established Clinical Data

Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes **(SELECT)**



Patients with preexisting **cardiovascular disease and overweight or obesity, but without diabetes**

Weekly 2.4 mg subcutaneous semaglutide **reduced cardiovascular death, nonfatal MI, or stroke** compared to placebo over a 39.8 month follow-up

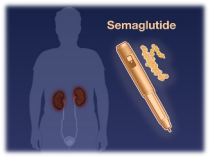
56

The New England Journal of Medicine. 2023;389(24):2221–2232.

56

Established Clinical Data

Effects of Semaglutide on Chronic Kidney Disease in Patients with Type 2 Diabetes **(FLOW)**



Patients with **preexisting chronic kidney disease and type 2 diabetes**

Weekly 1 mg subcutaneous semaglutide **reduced the risk of clinically important kidney outcomes and death from cardiovascular causes** compared to placebo over a 3.4 year follow-up

57

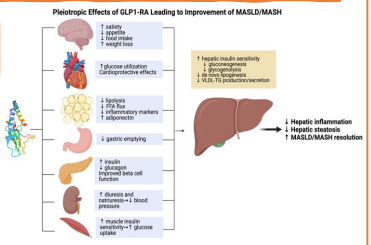
The New England Journal of Medicine. 2024;391(2):109–121.

57

Future Directions

Use for patients with fatty liver disease and non-alcoholic steatohepatitis?

Can decrease hepatic steatosis and promote liver regeneration by enhancement of fatty acid oxidation and modulation of hepatic lipid metabolism



58 Primary Care Diabetes. 2024;18(3):268–274. 58

58

Future Directions

Use for patients with early Alzheimer's disease?

May be neuroprotective by slowing disease progression, potentially improving cognitive function, reducing inflammation, and decreasing amyloid-beta plaque formations

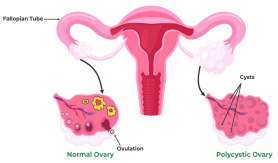
59 The Journal of the Alzheimer's Association. 2024;20(12):8661–8672. 59

59

Future Directions

Use for patients with polycystic ovary syndrome?

Improve insulin sensitivity, promote weight loss, lower androgen levels, and may restore menstrual regularity and ovulation



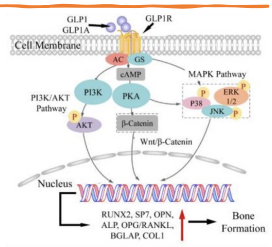
60 BMC Endocrine Disorders. 2023;23(1):1–33. 60

60

Future Directions

Use for patients with osteoporosis?

- Associated with increased bone mass, improved bone strength, and promotion of bone formation



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61

Future Directions

Use for patients with obstructive sleep apnea and obesity?

- Reduced hypoxic burden, hsCRP concentration, systolic blood pressure, and improved sleep-related patient-reported outcomes

62

62

New FDA Approval

Use for patients with obstructive sleep apnea and obesity?

- Reduced hypoxic burden, hsCRP concentration, systolic blood pressure, and improved sleep-related patient-reported outcomes

On 12/20/2024, the FDA approved Zepbound (tirzepatide) for **adults with moderate-to-severe obstructive sleep apnea and obesity**

63

Knowledge Check

What is a primary focus of current clinical trials evaluating GLP-1 and GIP medications?

A. Assessing the long-term effects of these medications on cardiovascular outcomes in patients with and without type 2 diabetes
B. Evaluating the efficacy of these medications in treating type 1 diabetes
C. Investigating the potential for these medications to cure obesity rather than manage it
D. Analyzing the cost-effectiveness of these medications in comparison to other traditional therapies

64

64

Knowledge Check

What is a primary focus of current clinical trials evaluating GLP-1 and GIP medications?

A. **Assessing the long-term effects of these medications on cardiovascular outcomes in patients with and without type 2 diabetes**
B. Evaluating the efficacy of these medications in treating type 1 diabetes
C. Investigating the potential for these medications to cure obesity rather than manage it
D. Analyzing the cost-effectiveness of these medications in comparison to other traditional therapies

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Final Remarks

GLP-1/GIP agonists enhance insulin secretion, slow gastric emptying, and increase satiety, with additional effects through pathways not yet fully understood

While these agents provide known impactful benefits, a risk-benefit discussion is essential prior to initiation as other indications and adverse effects have limited data

Current evidence supports the efficacy of these agents in improving blood glucose control and promoting weight loss

Ongoing research will provide additional insight on long-term outcomes and cardiovascular benefits as well as potential utility in metabolic disorders

66

66

References

- Aronne LJ, Sattar N, Horn DB, Bays HE, Wharton S, Lin WY, Ahmad NN, Zhang S, Liao R, Bunck MC, Jouravskaya I, Murphy MA, & SURMOUNT-4 Investigators. Continued Treatment With Tirzepatide for Maintenance of Weight Reduction in Adults With Obesity: The SURMOUNT-4 Randomized Clinical Trial. *JAMA*. 2024;331(1):38–48.
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Questions?

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69

Hormone Hangups with PCOS: Metabolic Treatment Modalities

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1/26/2025

29 Years Featuring
South Florida Pharmacy Residents

1

Objectives

1. Describe the pathophysiology of polycystic ovarian syndrome
2. Review management of polycystic ovarian syndrome
3. Develop a patient-specific treatment plan for a female with polycystic ovarian syndrome

2

Abbreviations

- AMH= anti-Müllerian hormone
- COC= combination oral contraceptive
- FSH= follicle stimulating hormone
- GLP= glucagon-like peptide
- GnRH= gonadotropin-releasing hormone
- IVF= in vitro fertilization
- LH= luteinizing hormone
- PCOS= polycystic ovarian syndrome
- SERM= selective estrogen receptor modulator
- SHBG= sex hormone binding globulin

3

Guidelines

- Endocrine Society 2023
- American College of Obstetricians & Gynecologists 2018
- American Association of Clinical Endocrinology 2015

4

Definition & Epidemiology

PCOS

- Characterized by hyperandrogenism, ovulatory dysfunction, and polycystic ovarian morphological features

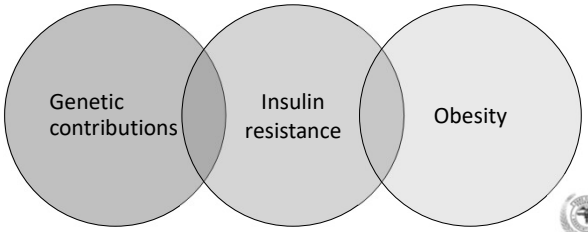
Prevalence

- 10-13%

McCartney CR, et al. *N Eng J Med.* 2016; 375: 54-64. ES 2023 Guidelines

5

Etiology



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Risk Factors

Family history	Metabolic disorder	Obesity
Sedentary lifestyle	Unhealthy diet	Teenage-early 20s

McCartney CR, et al. *N Eng J Med.* 2016; 375: 54-64.

7

Long-Term Risks

Cardiovascular Disease	Type 2 Diabetes	Endometrial Cancer	Infertility
Pregnancy Complications	Obstructive Sleep Apnea	Depression	Anxiety

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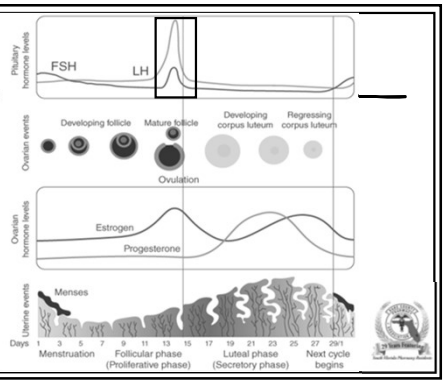
8

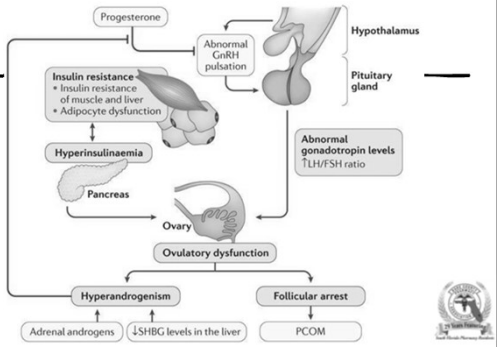
Menstrual Cycle



https://byjus.com/biology/menstrual-cycle/

9

PCOS Summary



Mardan S, et al. *KJPS*. 2617-2741.

10

Insulin Resistance

- Occurs in 50-80% of patients with PCOS
- Causes excess androgen production
- Reduces SHBG

McCartney CR, et al. *N Eng J Med*. 2016; 375: 54-64.

11

Clinical Presentation

- Hyperandrogenism
- Irregular menstruation
- Infertility
- Ovarian cysts
- Insulin resistance
- Obese
- Metabolic syndrome

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12

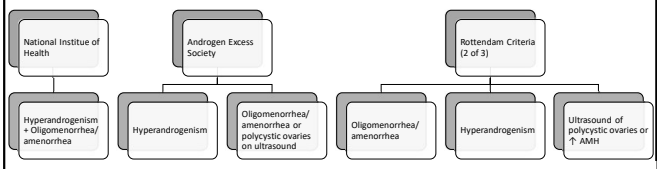
Laboratory & Objective Data

LH: ↑	FSH: ↓	Testosterone: ↑
Prolactin: ↓	SHBG: ↓	AMH: ↑

McCartney CR, et al. *N Eng J Med.* 2016; 375: 54-64.

13

Diagnosis



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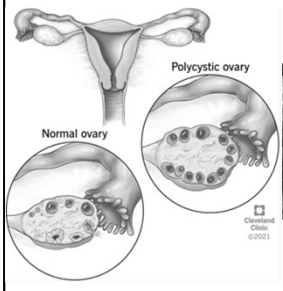

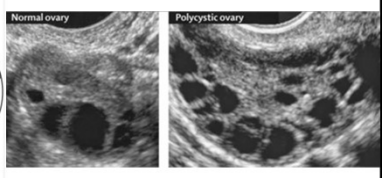

https://my.clevelandclinic.org/health/diseases/8316-polycystic-ovary-syndrome-pcos
https://www.drmoomjy.com/blog/pcos

15

Ferriman-Gallwey Score

4 grades of hirsutism

- <8 none
- 8-16 mild
- 17-25 moderate
- >25 severe

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Differential Diagnosis

Androgen secreting tumor	Cushing syndrome	Nonclassical congenital adrenal hyperplasia	Acromegaly
Primary hypothalamic amenorrhea	Primary ovarian failure	Thyroid disease	Prolactin disorders

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Which of the following is true regarding the pathophysiology?

A. ↑ FSH
B. ↑ progesterone
C. ↑ LH
D. ↓ GnRH pulse frequency

18

Which of the following is true regarding the pathophysiology?

A. ↑ FSH
B. ↑ progesterone
C. ↑ LH
D. ↓ GnRH pulse frequency

19

Non-Pharmacological Management

- Healthy diet
- Weight loss (5-10%)
- Exercise
- Smoking cessation
- Hair removal

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Medical Management

Key Questions:

- Are you currently desiring pregnancy?
- What symptoms are most bothersome?
- What is your past medical history?

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Medical Management

Combination oral contraceptives	Spironolactone	Metformin	Eflornithine
GLP-1 agonists	SGLT2i	Letrozole	Clomiphene

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22

Combination Oral Contraceptive (COC)

Dose	ADRs	MOA
• 20-30 µg of ethinyl estradiol + progestin (drospirenone, dienogest, cyproterone acetate)	• Hyperkalemia • Breast tenderness • Bloating • Weight gain • Break through bleeding	• Ethinyl estradiol- suppresses LH, which ↓ ovarian androgen production • Progestin- anti-androgen effects
Place in therapy	**Clinical Pearls**	**Warning & CI**
• 1st line • Not trying to conceive	• Hirsutism • Acne • Irregular menses	• Cigarette smoker + ≥ 35 years old • Thrombosis risk

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23

Spironolactone

Dose	ADRs	MOA
• 50-100 mg po bid	• Hyperkalemia	• Aldosterone antagonist • Competes with androgen for binding receptors
Place in therapy	**Clinical Pearls**	**Warning & CI**
• 2nd line • Given in addition to COC or unable to tolerate COC • Not trying to conceive	• Hirsutism • Acne • ~2-3 months for onset	• Pregnancy • K+ >5 • SCr ≥2 or eGFR <30

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24

Eflornithine

Dose	ADRs	MOA
• 13.9% cream • 1 application bid	• Burning • Stinging • Erythema • Rash	• Inhibits ornithine decarboxylase in human skin which reduces rate of hair growth
Place in therapy	**Clinical Pearls**	**Warning & CI**
• 2nd line add on	• Mild hirsutism • Applications should be at least 8 hours apart	• N/A

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GLP-1 Agonists

Dose	ADRs	MOA
• Semaglutide: 0.25 mg sc every 7 days (max 2.4 mg sc every 7 days) • Liraglutide: 0.6 mg sc daily (max 1.8 mg sc daily)	• Nausea, vomiting, diarrhea • Pancreatitis	• GLP-1 receptor activation ↑ insulin sensitivity which lowers androgen levels
Place in therapy	**Clinical Pearls**	**Warning & CI**
• Weight loss • Not in guidelines	• Insulin resistance • Irregular cycles • MACE benefit in other disease states	• Multiple endocrine neoplasia, type 2 (MEN 2) • Medullary thyroid cancer • Pregnancy

Elkind-Hirsch KE, et. al. *Fertil Steril.* 2022;118(2):276–284.

26

SGLT2i

Dose	ADRs	MOA
• Canagliflozin 100 mg daily • Dapagliflozin 10 mg daily • Empagliflozin 25 mg daily	• Urinary tract infection • Hypotension/ dizziness	• SGLT2i blocks reabsorption of glucose in the kidneys • Insulin sensitivity ↑, lowers blood glucose, and ↓ insulin levels
Place in therapy	**Clinical Pearls**	**Warning & CI**
• Not in guidelines	• Insulin resistance • MACE benefit in other disease states	• Euglycemic ketoacidosis • eGFR <25 (dapagliflozin) • eGFR <30 (empagliflozin and canagliflozin)

Javed Z, et al. *Clin Endocrinol.* 2019;90(6):802-811.

27

Metformin

Dose	ADRs	MOA
• 500 mg po daily • Max 2000 mg in adolescents • Max 2500 mg in adults	• Nausea, vomiting, diarrhea	• ↓ hepatic glucose output which ↓ insulin secretion • ↓ LH which ↓ androgen production in the theca cells
Place in therapy	**Clinical Pearls**	**Warning & CI**
• 1st line- insulin resistance • 2nd line- menstrual irregularities • Unable to tolerate COC • Add on to COC	• Increases fertility • Irregular cycles • Hirsutism	• Risk of ↓ vitamin B12

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Letrozole

Dose	ADRs	MOA
• 2.5 mg po x 5 days • Start on days 3, 4, or 5 following menses • May increase to 5 mg and 7.5 mg • May repeat for 6 cycles	• Arthralgia • Bone pain • Weakness • Fatigue • Hot flashes • Nausea	• Inhibits aromatase which prevents testosterone from being converted to estrogen • Reduced estrogen signals to the pituitary to release FSH which stimulates ovulation
Place in therapy	**Clinical Pearls**	**Warning & CI**
• 1st line- infertility	• Drug of choice for anovulatory infertility	• CNS depression

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29

Clomiphene

Dose	ADRs	MOA
• 50-100 mg po x 5 days • Start on day 5 following menses • May repeat for 6 cycles	• Hot flashes • Nausea • Mood swings	• SERM • Blocks circulating estrogen and negative feedback to hypothalamus
Place in therapy	**Clinical Pearls**	**Warning & CI**
• 2nd line for infertility • Can be combined with metformin	• May reduce dose to 25 mg if history of ovarian cysts	• Discontinue if visual changes occur

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30

GnRH Agonists

Dose	ADRs	MOA
• Leuprolide 1 mg sc daily • Nafarelin 0.5 mg sc daily	• Hot flashes • Mood swings • Headache • Breast tenderness	• Continually stimulates GnRH receptors to ↓ gonadotropin release • Initially causes a burst of gonadotropins then ↓
Place in therapy	**Clinical Pearls**	**Warning & CI**
• Anovulatory infertility	• Can result in false negative pregnancy tests	• Metabolic syndrome

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31

GnRH Antagonists

Dose	ADRs	MOA
• Cetrorelix 0.25 mg sc daily • Ganirelix 0.25 mg sc daily	• Headache • Abdominal pain	• Block GnRH receptors to cause rapid ↓ of GnRH release • Prevent premature LH surge
Place in therapy	**Clinical Pearls**	**Warning & CI**
• Anovulatory infertility	• Can result in false negative pregnancy tests	• Metabolic syndrome

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32

Select all that apply: Which options can be used to regulate menses in PCOS in a patient not trying to conceive?

A. Ethinyl estradiol + drospirenone
B. Clomiphene
C. Letrozole
D. Metformin

33

Select all that apply: Which options can be used to regulate menses in PCOS in a patient not trying to conceive?

A. Ethinyl estradiol + drospirenone
B. Clomiphene
C. Letrozole
D. Metformin

34

Efficacy of an oral contraceptive containing drospirenone in the treatment of women with polycystic ovary syndrome

Study Design
- Prospective open-label trial

Objective
- Assess the efficacy of ethinyl estradiol & drospirenone in PCOS

Method
- Ethinyl estradiol & drospirenone in PCOS

35

Efficacy of an oral contraceptive containing drospirenone in the treatment of women with polycystic ovarian syndrome

Primary Outcomes
- Change in testosterone level
- Ferriman-Gallwey (F-G) Score

Secondary Outcome
- Clinical changes
- Biochemical changes
- Hormonal changes

Pehlivanov B, et al. *Eur J Contracept Reprod Health Care.* 2009;14(1):30-35.

36

Efficacy of an oral contraceptive containing drospirenone in the treatment of women with polycystic ovarian syndrome

Results	Baseline	After 6 cycles	P value
Testosterone (nmol/L)	6.18 ± 0.26	5.15 ± 0.28	**P<0.05**
F-G Score	11.6 ± 0.9	9.05 ± 0.46	**P<0.05**
BMI (kg/m^2)	26.45 ± 0.65	25.97 ± 0.6	P>0.05
Free androgen index	18.77 ± 1.85	4.18 ± 0.95	**P<0.001**

Pehlivanov B, et al. *Eur J Contracept Reprod Health Care.* 2009;14(1):30-35.

37

Efficacy of an oral contraceptive containing drospirenone in the treatment of women with polycystic ovarian syndrome

Take Home Message

- Efficacious on surrogate markers in PCOS
- Weight Neutral
- Option for patients not trying to conceive

Pehlivanov B, et al. *Eur J Contracept Reprod Health Care.* 2009;14(1):30-35.

38

Liraglutide 3 mg on weight, body composition, hormonal, and metabolic parameters in women with obesity and PCOS

Study Design

- Randomized, double-blind, placebo-controlled study

Objective

- Assess efficacy and safety of liraglutide compared to placebo for reduction of body weight and hyperandrogenism in women with obesity and PCOS

Method

- Liraglutide 3 mg sc daily versus placebo + lifestyle modification

Elkind-Hirsch KE, et. al. *Fertil Steril.* 2022;118(2):276–284.

39

Liraglutide 3 mg on weight, body composition, hormonal, and metabolic parameters in women with obesity and PCOS

Primary Outcomes

- Body weight change
- Change in bioavailable testosterone

Secondary Outcomes

- Menstrual frequency
- Adverse Drug Reactions

Elkind-Hirsch KE, et. al. *Fertil Steril.* 2022;118(2):276–284.

40

Liraglutide 3 mg on weight, body composition, hormonal, and metabolic parameters in women with obesity and PCOS

Results	Liraglutide	Placebo	P value
Body weight change (kg)	-6.3 ± 2.9	-1.1 ± 5	**P=0.002**
Bioavailable testosterone (ng/dL)	-0.92 ± 0.6	+0.8 ± 0.75	**P=0.006**
Menstrual frequency/ year	+4.15 ± 0.4	0 ± 0.7	**P=0.0001**
Nausea (%)	25.5 %	11.1 %	**P<0.05**

Elkind-Hirsch KE, et. al. *Fertil Steril.* 2022;118(2):276–284.

41

Liraglutide 3 mg on weight, body composition, hormonal, and metabolic parameters in women with obesity and PCOS

Take Home Message

- Efficacious on both clinical and surrogate markers in PCOS
- Proven weight loss
- Major adverse cardiovascular event reduction is not established in PCOS
- Option for patients not trying to conceive

Pehlivanov B, et al. *Eur J Contracept Reprod Health Care.* 2009;14(1):30-35.

42

Effects of empagliflozin on metabolic parameters in polycystic ovary syndrome: A randomized controlled study

Study Design

- Open-label, randomized study

Objective

- Compare efficacy and safety of empagliflozin versus metformin in patients with PCOS

Javed Z, et al. *Clin Endocrinol.* 2019;90(6):802-811.

43

Effects of empagliflozin on metabolic parameters in polycystic ovary syndrome: A randomized controlled study

Method

- Empagliflozin 25 mg daily vs. metformin SR 1500 mg daily for 12 weeks

Outcomes

- BMI reduction
- Hormonal and metabolic changes

Javed Z, et al. *Clin Endocrinol.* 2019;90(6):802-811.

44

Effects of empagliflozin on metabolic parameters in polycystic ovary syndrome: A randomized controlled study

Results	Empagliflozin	Metformin	P value
BMI reduction	-1.4% ± 3.2%	+1.1 ± 2.2%	**P=0.006**
Testosterone (nmol/L)	0 ± 0.2	-0.2 ± 1.2	P>0.05
SHBG (nmol/L)	1.9 ± 0.23	0 ± 0.15	**P=0.049**

Javed Z, et al. *Clin Endocrinol.* 2019;90(6):802-811.

45

Effects of empagliflozin on metabolic parameters in polycystic ovary syndrome: A randomized controlled study

Take Home Message

- Empagliflozin had a greater decrease in SHBG compared to metformin
- Statistically significant weight loss
- Option for patients not trying to conceive

Pehlivanov B, et al. *Eur J Contracept Reprod Health Care.* 2009;14(1):30-35.

46

Letrozole versus clomiphene for infertility in the polycystic ovary syndrome

Study Design

- Double-blind, multicenter, randomized control trial

Objective

- Assess if letrozole compared to clomiphene has improved safety and efficacy for infertility treatment with PCOS

Legro RS, et al. *N Engl J Med.* 2014;371:119-129.

47

Letrozole versus clomiphene for infertility in the polycystic ovary syndrome

Method

- Letrozole 2.5 mg vs. clomiphene 50 mg

Primary Outcome

- Live births

Secondary Outcomes

- Ovulation
- Pregnancy loss
- Singleton birth
- Congenital abnormalities

Legro RS, et al. *N Engl J Med.* 2014;371:119-129.

48

Letrozole versus clomiphene for infertility in the polycystic ovary syndrome

Results	Letrozole	Clomiphene	P value
Live births	27.5%	19.1%	**P=0.007**
Ovulation	88.5%	76.6%	**P<0.001**
Pregnancy loss	31.8%	29.1%	P=0.65
Singleton birth	96.1%	93.1%	P=0.49
Congenital abnormalities	3.9%	1.5%	P=0.65

Legro RS, et al. *N Engl J Med.* 2014;371:119-129.

49

Letrozole versus clomiphene for infertility in the polycystic ovary syndrome

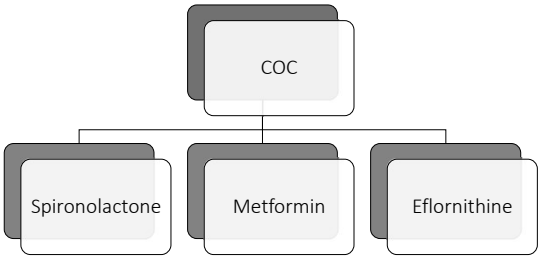
Take Home Message

- Letrozole is superior to clomiphene for infertility treatment due to PCOS
- Increased live births and ovulation in letrozole compared to clomiphene
- No difference in pregnancy loss, multiple births, or congenital abnormalities

Pehlivanov B, et al. *Eur J Contracept Reprod Health Care.* 2009;14(1):30-35.

50

Algorithm: PCOS not conceiving



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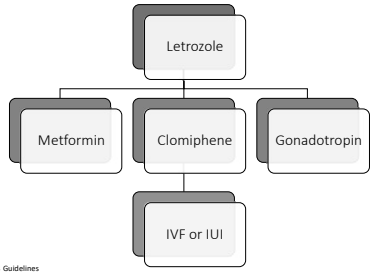
Algorithm: Infertility in PCOS



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Drug	Oligo/ Amenorrhea	Hirsutism/ Acne	Infertility	Weight Loss	Insulin Resistance
COC	X	X			
Spironolactone		X			
Eflornithine		X			
SGLT2i					X
GLP-1 agonists	X			X	X
Metformin	X	X	X		X
Letrozole			X		
Clomiphene			X		
Gonadotropin			X		

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53

Which is the best treatment option for the patient who is not trying to conceive?

A. COC
B. Liraglutide
C. Eflornithine
D. Metformin

36 YO female with PMH: PCOS (acne, hirsutism)
- BMI: 32 kg/m^2
- Social hx:
  - (+) smoking
- Family hx:
  - Mother-Type 2 diabetes and hypertension
  - Father-MEN 2

54

Which is the best treatment option for the patient who is not trying to conceive?

A. COC
B. Liraglutide
C. Eflornithine
D. Metformin

36 YO female with PMH: PCOS (acne, hirsutism)
- BMI: 32 kg/m^2
- Social hx:
  - (+) smoking
- Family hx:
  - Mother-Type 2 diabetes and hypertension
  - Father-MEN 2

55

Pharmacist Take Home Points

COC
- Multiple indications
- Progesterone must be an antiandrogen (drospirenone, dienogest, cyproterone acetate)

Spironolactone
- Higher doses compared to heart failure and hypertension
- 50-100 mg po bid

Eflornithine
- Add on therapy only
- Mild hirsutism

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Pharmacist Take Home Points

GLP-1 agonists
- Not in guidelines or FDA approved

SGLT2i
- Not in guidelines or FDA approved

Metformin
- Only PCOS drug that can be used regardless of pregnancy desire

57

Pharmacist Take Home Points

Letrozole

- Duration is 5 days per cycle

Clomiphene

- Duration is 5 days per cycle

GnRH Agonists & Antagonists

- False negative pregnancy tests

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Conclusion

Prevalence of PCOS has increased

Patient education is essential

Treatment is based on the patient's symptoms and preferences

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Hormone Hangups with PCOS: Metabolic Treatment Modalities

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