The KIDs List: Agents to Avoid and Use with Caution in Children

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Financial Disclosure and Resolution

Under guidelines established under the Standards for Integrity and Independence in Accredited Continuing Education, disclosure must be made regarding relevant financial relationships with ineligible companies within the last 24 months.

- I have no relevant financial relationships with ineligible companies to disclose.
- I will be discussing off-label use of medications that are not approved indications by the FDA

Professional Practice Gap

- Many medications used off-label in children
- PK differences between neonates, infants, children, and adults may result in differences in dosing, efficacy, and safety
- Knowledge about medications that should be avoided or used with caution may be limited for those with less involvement in care of pediatric patients
- Pharmacist lack of knowledge may result in:
  - Inadvertently dispensing a medication that should be avoided
  - Refusal to dispense a medication that has a relative contraindication
  - Inadequate provision of medication counseling

Learning Objectives

At the completion of this activity, pharmacists will be able to:

1. Identify the purpose of the KIDs List
2. Explain why use of benzocaine, codeine, diphenoxylate/atropine, and valproic acid should be avoided in infants and/or children
3. Describe why ceftriaxone, loperamide, sulfamethoxazole/trimethoprim, and tetracyclines should be used with caution in infants and/or children

Pre-Assessment Question #1

When poll is active, respond at **pollev.com/ou321**
Text **OU321** to **37607** once to join

Which of the following is an age-related pharmacokinetic difference that is observed in the neonatal population compared with older children?

- Increased absorption of medications administered intramuscularly
- Increased dermal absorption of topically applied medications
- Decreased enteral absorption of acid-labile medications
- Decreased volume of distribution of hydrophilic medications

Pre-Assessment Question #2

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A parent of an 8 month-old child presents to the pharmacy with 4 new prescriptions for the child. For which of the following prescriptions should the pharmacist call the provider to recommend an alternative agent since it is recommended to avoid use?

- Sulfamethoxazole/trimethoprim
- Clotrimazole/betamethasone
- Doxycycline
- Aspirin

Pre-Assessment Question #3

Adverse Drug Reactions in Pediatrics

- Incidence and prevalence of ADRs higher in children compared to adults
- Neonates at highest risk for ADRs
- Factors associated with increased risk for ADRs:
  - Off-label use of 50% of medications on the U.S. market
  - Reliance on anecdotal experience, case reports, under-powered studies, and historical dogma
  - Age-related differences in absorption, metabolism, distribution, and elimination of medications

ADME Differences in Neonates

Absorption	Distribution
• PO absorption ↓ or ↑ - ↑ gastric pH - ↑ gastric emptying time - ↓ intestinal motility • ↑ dermal absorption • ↓ intramuscular absorption	• ↑ water-to-fat ratio • ↓ plasma protein binding
Metabolism	**Elimination**
• Phase I reactions ↓ • Phase II reactions - Sulfation (functional) - Methylation (functional) - Glucuronidation (↓) - Glycine conjugation (↓)	• ↓ Glomerular filtration rate • ↓ tubular secretion & reabsorption

Lim SY, Pettit RS. *Am J Health-Syst Pharm.* 2019; 76:1472-80.

Issues with Medications in Children

- Uncertainty of appropriate dose to initiate – may extrapolate doses from older population
- Differences in ADME may increase risk for toxicity – active ingredient or excipients
- Historical dogma may result in avoidance of some agents and increased use of suboptimal agents
- Many prescribers/pharmacists unfamiliar with agents to avoid/use with caution – not readily accessible in a single reference

KIDs List

KIDs List

- Key Potentially Inappropriate Drugs in Pediatrics
- Commissioned by the Pediatric Pharmacy Association
- Published in the Journal of Pediatric Pharmacology and Therapeutics in March 2020
- List includes:
  - 67 medications/medication classes
  - 10 excipients

Meyers RS, et al. *J Pediatr Pharmacol Ther* 2020;25(3):175-191.

Definitions in the KIDs List

Term	Definition
Recommendation	
Avoid	Strong recommendation; potentially life-threatening or life-altering
Caution	Low strength of recommendation; low quality of evidence; clear therapeutic need for a medication in spite of higher ADR risk
Strength of Recommendation	
Strong	When presented with ADR, would choose to avoid or use with caution vs. risking development of ADR
Weak	Consistent with significant variability, decision may differ based on situation or patient/caregiver preference
Age Definitions	
Neonate	<1 month
Infant	< 24 months
Child	< 18 years

Purpose of KIDs List

- Reference tool to identify medications with high risk of ADRs in children
- Identify areas for research in children
- Serve as a catalyst to improve medication safety in children
- Enhance public awareness of medications to avoid or use in caution in children

Meyers RS, et al. *J Pediatr Pharmacol Ther* 2020;25(3):175-191.

Agents to Avoid

Agents to Avoid

- Total of 34 agents recommended to avoid use
- Breakdown of population for ‘avoid use’ designation:
  - Neonates (n=13)
  - Infants (n=12)
  - Children (n=9)
- Commonly used agents with ‘avoid use’ designation:
  - Benzocaine/lidocaine
  - Codeine
  - Diphenoxylate/atropine
  - Lindane
  - Loperamide
  - Mineral oil
  - Sulfamethoxazole
  - High potency topical corticosteroids
  - Valproic acid

Benzocaine

- KIDs List Rating:

Risk/Rationale	Recommendation	Strength of Recommendation	Quality of Evidence
Methemoglobinemia	Avoid in infants for teething or pharyngitis	Strong	High

- FDA issued communications:
  - 2011 - Boxed warning to avoid use of topical benzocaine in children < 2 years
  - 2018 – Products marketed for use in children will be removed from market
- Avoid use: minimal benefit, associated with methemoglobinemia and arrythmias

Meyers RS, et al. *J Pediatr Pharmacol Ther* 2020;25(3):175-191.
https://www.fda.gov/news-events/press-announcements/fda-takes-action-against-use-otc-benzocaine-teething-products-due-serious-safety-risk-lack-benefit

Recommendations for Teething Pain

- Many teething products for babies are now “benzocaine free”
  - Common ingredients: water, sorbitol, propylene glycol, glycerin, cellulose gum, poloxamer 407, flavor, potassium sorbate, simethicone, sodium saccharin, citric acid
  - Night-time formulations: addition of chamomile
- Avoid use of homeopathic teething tablets
  - Not been evaluated for safety or efficacy
  - FDA has identified elevated amounts of belladonna alkaloids (atropine, scopolamine) in some products
- Alternative recommendations:
  - Massage the gums
  - Teething rings (firm rubber, not products you freeze)
  - Occasional use of acetaminophen or ibuprofen

https://www.fda.gov/consumers/consumer-updates/safely-soothing-teething-pain-and-sensory-needs-babies-and-older-children
https://www.fda.gov/news-events/press-announcements/fda-confirms-elevated-levels-belladonna-certain-homeopathic-teething-products

Codeine

- KIDs List Rating:

Risk/Rationale	Recommendation	Strength of Recommendation	Quality of Evidence
Respiratory depression, death	Avoid in children unless pharmacogenetic testing is used	Strong	High

- FDA issued communications:
  - 2013 – New boxed warning, contraindicated to use for pain control following tonsillectomy and/or adenoidectomy
  - 2017 – Mandated labeling changes:
    - Contraindicated for pain or cough in all children ≤ 12 years
    - Warning to avoid use in children 12-18 years who are obese or have sleep apnea
    - Warning to avoid use in mothers that are breastfeeding
  - 2018 – Contraindicated for cough in children ≤ 18 years

http://wayback.archive-it.org/7993/20170722185707/https://www.fda.gov/Drugs/DrugSafety/ucm339112.htm
https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-restricts-use-prescription-codeine-pain-and-cough-medicines-and
https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-requires-labeling-changes-prescription-opioid-cough-and-cold

Issues with Codeine & Other Opioids

- Pro-drug metabolized by CYP2D6 to morphine
- Interpatient variability in metabolism = variability in response:
  - Ultra-rapid metabolizers – increased risk for toxicity
  - Poor metabolizers – limited analgesic efficacy
- Alternative opioids for analgesia:
  - Hydrocodone – prodrug metabolized by CYP2D6, included in 2018 FDA updates & contraindicated for cough
  - Oxycodone – not a prodrug, primarily metabolized by CYP3A4, but CYP2D6 is minor pathway (oxycodone → oxymorphone)
  - Morphine – metabolized by glucuronidation, not by CYP2D6

Tramadol

- KIDs List Rating:

Risk/Rationale	Recommendation	Strength of Recommendation	Quality of Evidence
Respiratory depression	Caution in children unless pharmacogenetic testing is used	Weak	Low

- FDA issued communications:
  - 2015 – FDA investigating risk of respiratory depression children < 17 years
  - 2017 – FDA mandates labeling changes:
    - Contraindicated for pain in all children ≤ 12 years
    - Contraindicated for pain after tonsillectomy/adenoidectomy in children < 18 years
    - Warning to avoid use in children 12-18 years who are obese or have sleep apnea
    - Warning to avoid use in mothers that are breastfeeding

https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-restricts-use-prescription-codeine-pain-and-cough-medicines-and
https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-evaluating-risks-using-pain-medicine-tramadol-children-aged-17-and

Tramadol

- Use ↑ after codeine was contraindicated in 2013
- Also a prodrug metabolized by CYP2D6 to *O*-desmethyltramadol
- Similar issues to codeine with variability in metabolism and response
- FDA warning based on 9 cases of respiratory depression, including 3 deaths, in children
  - Most occurred within 24 hours of tramadol initiation
  - All three deaths in children < 6 years of age
- Some experts recommend use for chronic pain if pharmacogenetic testing can be performed

Obeng AO, et al. Pharmacotherapy 2017;37(9):1105-1121.

Diphenoxylate/Atropine

- KIDs List Rating:

Risk/Rationale	Recommendation	Strength of Recommendation	Quality of Evidence
Respiratory depression, death	Avoid in <6 years	Strong	Moderate

- Labeling for use: Tablets (≥ 13 years), liquid (≥ 2 years)
- Package insert states use is contraindicated for children < 6 years – respiratory and CNS depression
- Fatalities and toxicities reported in infants and children
- Greatest risk in children < 6 years who receive repetitive doses, incorrect dose, or inadvertent ingestion

Thomas TJ, et al. *J Emerg Med* 2008;34(1):71-75.
https://labeling.pfizer.com/ShowLabeling.aspx?id=629. Accessed September 4, 2022.

Loperamide

- KIDs List Rating:

Risk/Rationale	Recommendation	Strength of Recommendation	Quality of Evidence
Ileus, lethargy	Avoid in infants for acute infectious diarrhea	Strong	High

- Package insert states contraindicated in children ≤ 2 years
- Meta-analysis of 12 studies of loperamide use in children < 12 years (n=927 patients)
  - ADEs reported in 10.1% of patients
  - Serious ADEs (ileus, lethargy, or death) reported in 0.9% of patients (all ≤ 3 years of age)

Anti-Motility Agent Recommendations

- Oral rehydration solutions and early refeeding should remain focus of management of diarrhea in young children
- Loperamide preferred as adjunct therapy over diphenoxylate/atropine in non-infectious diarrhea
- Avoid use of anti-motility agents in children if infectious diarrhea suspected

Topical Corticosteroids (Group I-III)

- KIDs List Rating:

Risk/Rationale	Recommendation	Strength of Recommendation	Quality of Evidence
Adrenal suppression, higher rate of systemic absorption in children vs. adults	Avoid in <1 year for diaper dermatitis	Strong	Low

- Topical steroids classified based on potency (i.e., Group I-VII)
  - Determined by vasoconstrictive effects
  - Potency dependent upon characteristics of steroid, concentration of steroid, and vehicle of product

Examples Topical Corticosteroid Potency

Potency (Group)	Medication	Brand Name	Dosage Vehicle
Super potent (Group I)	Augmented betamethasone dipropionate 0.05% Clobetasol propionate 0.05%	Diprolene Temovate	Gel, Oint Cream, Gel, Oint
High potency (Group II)	Augmented betamethasone dipropionate 0.05% Betamethasone dipropionate 0.05%	Diprolene Diprosone	Cream, Lotion Oint
Mid-potency (Group III)	Betamethasone dipropionate 0.05% Triamcinolone acetonide 0.5%	Betanate Cinalog	Cream Cream, Oint
Mid to low-mid potency (Group IV-V)	Betamethasone valerate 0.1% Mometasone furoate 0.1% Hydrocortisone valerate 0.2%	Beta-Val Elocon Westcort	Cream, Lotion Cream, Lotion, Oint Cream, Oint
Mild potency (Group VI)	Desonide 0.05% Hydrocortisone butyrate 0.1%	Desonate Locoid	Gel Cream
Low potency (Group VII)	Hydrocortisone 1%, 2.5%	-----	Cream, Lotion, Oint

Topical Corticosteroids Recommendations

- Use lowest potency steroid for the shortest duration of time
- Discontinue topical steroid immediately after resolution of erythema
- Recommend Group VI and VII topical corticosteroids in diaper area for 3-10 days
- Combination antifungal/steroid products should NOT be used in children:
  - Lotrisone (betamethasone/clotrimazole)
  - Mycolog II (triamcinolone/nystatin)

Valproic Acid

- KIDs List Rating:

Risk/Rationale	Recommendation	Strength of Recommendation	Quality of Evidence
Pancreatitis, fatal hepatotoxicity	Avoid in infants Caution in < 6 years	Strong	High

- Boxed warning for increased risk of fatal hepatotoxicity, specifically in children ≤ 2 years
- 2014 report of VigiBase reports:
  - 66.7% pf cases involved children < 6 years
  - ≥ 2.5-times greater number reports than expected in children < 6 years
  - Highest rate noted in children 1-2 years
  - Median time to onset – 66 days (IQR, 38.8-121.5)

Star K, et al. *PLOSone* 2014;9(10):e108970.

Recommendations for Valproic Acid

- Avoid use in children ≤ 2 years
- Recommendations if used in children < 6 years:
  - Avoid polytherapy
  - Monitor for non-specific symptoms including malaise, weakness, lethargy, facial edema, anorexia, and vomiting
  - Recommend to monitor LFTs at baseline and frequent intervals while on therapy (especially in first 6 months)

Star K, et al. *PLOSone* 2014;9(10):e108970.

Sulfamethoxazole/Trimethoprim (SMX/TMP)

- KIDs List Rating:

Risk/Rationale	Recommendation	Strength of Recommendation	Quality of Evidence
Kernicterus	Avoid in neonates	Weak	Very low

- Package inert – contraindicated if < 2 months of age
  - Highly protein bound
  - Concern about displacement of bilirubin → kernicterus
- Evidence behind recommendation weak & quality of evidence is very low

Evidence Behind Recommendation

- Sulfisoxazole causes bilirubin displacement from albumin binding sites and ↑ risk for kernicterus
  - Landmark study in 1956 of sulfisoxazole vs. oxytetracycline, ↑ rate kernicterus, 64% vs. 0%
  - In-vitro and animal studies confirmed bilirubin displacement with sulfisoxazole
- No studies have demonstrated association with SMX and bilirubin displacement/kernicterus
  - Less displacement of bilirubin with SMX vs. other sulfonamides
  - SMX serum concentration of 400 mcg/mL needed to displace bilirubin significantly – 10-20 times therapeutic conc reached

SMX = sulfamethoxazole

Thyagarajan B, et al. *Drug Chem Toxicol* 2014;37(2):121-129.

Recommendation

- Most experts believe there is a *relative contraindication* for use of SMX/TMP in infants < 2 months
- Relative comfort with use in patients 1-2 months of age
  - Obtain baseline total bilirubin concentration
  - Monitor total bilirubin concentration during course of treatment
- Consider use in patients 0.5-1 month of age if clinically needed and no alternative agent available

Agents to Use with Caution

Agents to Use with Caution

- Total of 16 agents recommended to use with caution
- Breakdown of population for 'caution' designation:
  - Neonates (n=4)
  - Infants (n=1)
  - Children (n=11)
- Commonly used agents with 'caution' designation:
  - Aspirin
  - Camphor
  - Ceftriaxone
  - Chlorhexidine
  - Daptomycin
  - Lamotrigine
  - Olanzapine
  - Promethazine
  - Tetracyclines
  - Tramadol

Ceftriaxone

- KIDs List Rating:

Risk/Rationale	Recommendation	Strength of Recommendation	Quality of Evidence
Kernicterus	Caution in neonates	Weak	Very low

- Package insert – contraindicated for use in neonates
  - Highly protein bound (85-95%) agent
  - Concern about displacement of bilirubin → kernicterus
- Contraindication for use primarily based on in-vitro data

Evidence Behind Recommendation

- Initial in-vitro studies demonstrated displacement of bilirubin from albumin binding sites
- 7 small clinical studies demonstrate relative safety with use:
  - Initial increase in serum bilirubin, but decreases after infusion
  - 0-20% with ↑ serum bilirubin & required discontinuation
  - No patient in clinical studies have developed kernicterus
- Recent cefotaxime shortage prompted use of alternate third-generation cephalosporins
  - Some experts suggest ceftriaxone can be used in healthy term or near-term neonates with mild hyperbilirubinemia

Donnelly PC, et al. *Pediatr Drugs* 2017;19:21-34.
Hile GB, et al. *J Pediatr Pharm Ther* 2021;26(1):99-103.

Ceftriaxone/Calcium FDA Alerts

Date	FDA Alert
July 2007	- Should not be reconstituted with calcium-containing solutions (e.g., Lactated Ringer's) - Should not be administered concurrently with IV calcium-containing products in neonates
September 2007	- Previous warning extended to include adult patients - Should not administer within 48 hours of IV calcium-containing products
April 2009	- Ceftriaxone and calcium-containing IV products can be used concomitantly in patients > 28 days of age - Concomitant use of calcium-containing IV products is contraindicated in patients ≤ 28 days - Must not be administered simultaneously with IV calcium-containing solutions via Y-site in any age group

Bradley JS, Bocchini JA. *AAP News* 2009;30(6).
Meyers RS, et al. *J Pediatr Pharmacol Ther* 2020; 25(3):175-191.

Tetracyclines

- KIDs List Rating:

Risk/Rationale	Recommendation	Strength of Recommendation	Quality of Evidence
Tooth discoloration & enamel hypoplasia	Caution in < 8 years	Strong	High
Retardation of skeletal development	Neonates	Strong	Moderate

- Package insert – Use in children < 8 years of age only when benefits outweigh risks
  - Tooth staining reported since 1950's, 23-92% of exposed children
  - Decrease in bone growth observed in exposed neonates
- Predominantly associated with 1st generation tetracyclines – greater affinity for binding calcium

Todd SR, et al. *J Pediatr* 2015;166(5):1246-1251.
American Academy of Pediatrics. Red Book 2021.

Doxycycline

- Second generation tetracycline
- No reports of dental staining with doxycycline in young children
- Retrospective cohort study of doxycycline-exposed (n=58) versus non-exposed children (n=213)
  - No visible teeth staining observed
  - Exposure to doxycycline not associated with enamel hypoplasia
- Recommendations for use:
  - AAP and CDC recommend doxycycline as agent of choice for tickborne diseases
  - AAP states doxycycline can be used for short duration (i.e., $\leq$ 21 days) in all children

AAP = American Academy of Pediatrics
CDC = Center for Disease Control and Prevention

Todd SR, et al. *J Pediatr* 2015;166(5):1246-1251.
American Academy of Pediatrics. Red Book 2021.

Aspirin

- Historically avoided because of risk for Reye syndrome in children with viral infections
- Recent literature has contested the association of aspirin with Reye syndrome – likely related to genetic disorders of metabolism
- Recommended for use in specific patients where benefit is greater than risks

Medications That Did Not Make the List

Fluoroquinolones

- Historical recommendation to avoid use in children < 18 years due to concern for cartilage disruption
- Evidence to support avoidance of use not robust, based on animal data but not observed in clinical use
- Not routinely first-line agents, but can be used in children of all ages if needed

Sildenafil

- FDA issued boxed warning (2012) to avoid use in children based on a RCT showing:
  - High sildenafil dose associated with higher risk of death
  - Low sildenafil dose not shown to be effective
- Experts questioned decision, concerns about clinical implication
- FDA clarifies warning (2014), purpose was to raise awareness, but not intended to state should *never* be used
- Conservative sildenafil dosing recommended:

Patient weight	Recommended dose
< 8 kg	0.5-1 mg/kg TID
8-20 kg	10 mg TID
> 20 kg	20 mg TID

Abman SH, et al. *Am J Respir Crit Care Med* 2013;166(5):1246-1251.
Avitabile CM, et al. *Pediatr Drugs* 2020;22(2):123-147.

Antidepressants

- FDA issued boxed warning in 2004 for entire class, increased risk of suicidality and suicidal ideation in children
- Criticism of warning by experts, lead to undertreatment of children with depression
- Based on recent studies, risk appear to be increased with antidepressants, but can be clinically beneficial as well
- Difficult to identify if one drug has greater risk than others
- Provide counseling of risk and monitor closely

Spielmans GI SH, et al. *Front Psychiatry* 2020;11(18):doi: 10.3389/fpsyt.2020.00018.
Fornaro M, et al. *Front Psychiatry* 2019;10 (294):doi: 10.3389/fpsyt.2019.00294.

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- Sulfamethoxazole/trimethoprim
- Clotrimazole/betamethasone
- Doxycycline
- Aspirin

Post-Assessment Question #3

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A parent of an 11 month-old infant is looking at non-prescription products for teething pain. Which of the following can be recommended for this child?

- Benzocaine (Oragel)
- Hyland's teething products
- Ibuprofen (Motrin)
- Acetaminophen with codeine

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Conclusion and Clinical Pearls

- KIDs List is beneficial to prescribers and pharmacists:
  - Tool to improve drug safety for children
  - Can serve as a quick reference of medications that should be avoided and used with caution in pediatric patients
  - Highlights knowledge gaps and level of evidence in the literature
- Several drugs on list with 'weak' recommendations – so more extensive exploration needed
- Further study needed for medications with conflicting evidence that were not included on list

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