JPPT | 2025 KIDs List

Pediatric Pharmacy Association 2025 KIDs List of Key Potentially Inappropriate Drugs in Pediatrics

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OBJECTIVE The objective was to update the KIDs List, a list of drugs and excipients that are potentially inappropriate for use in pediatric patients, accounting for emerging pharmacologic agents and published evidence.

METHODS A panel of 12 pediatric pharmacists from the Pediatric Pharmacy Association (PPA) evaluated primary, secondary, and tertiary literature; FDA Pediatric Safety Communications; the UpToDate Lexidrug database; and product information for drugs that may be considered potentially inappropriate for use in pediatric patients. A PubMed search identified new publications from October 1, 2017, to November 1, 2023. All agents included in the previous publication and those anecdotally identified as candidates for the list by the authors or PPA members were evaluated. Evidence was reviewed by all authors. The draft list underwent a 30-day public comment period prior to being finalized.

RESULTS A PubMed search yielded 917 unique titles of which 17 were deemed relevant for full review. Sixty-seven drugs and/or drug classes and 10 excipients from the original publication were also reviewed. Author and PPA member recommendations highlighted an additional 25 drugs or drug classes. The UpToDate Lexidrug database extraction yielded 1470 drugs, which were filtered to 145 agents for author review. After critical analysis and reorganization, the second edition of the KIDs List contains 39 drugs and/or drug classes and 10 excipients.

CONCLUSIONS This article updates the initial list of drugs and excipients that are potentially inappropriate for prescribing in all or a select subgroup of pediatric patients. The second edition should stimulate novel research to inform future updates.

ABBREVIATIONS AAP, American Academy of Pediatrics; ADR, adverse drug reaction; BPCA, Best Pharmaceuticals for Children Act; ED, emergency department; FDA, US Food and Drug Administration; MeSH, Medical Subject Headings; NSAIDs, nonsteroidal anti-inflammatory drugs; PPA, Pediatric Pharmacy Association; PREA, Pediatric Research Equity Act; WHO, World Health Organization

KEYWORDS adverse drug event; adverse drug reaction; excipients; medications; pediatrics; potentially inappropriate medication list

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Introduction

Adverse drug reactions (ADRs) represent a significant health care burden. Every year, 6 of every 1000 adults will visit the emergency department (ED) for an ADR.[1] Nearly 40% of these visits prompt hospitalization, a setting in which serious ADRs occur in 6.7% of patients with a fatality rate of 0.32%, representing a top-10 cause of death.[2] Specific subpopulations experience higher risk, including those at the extremes of the age spectrum.[3] Serious ADRs account for up to 4% of pediatric hospitalizations and occur in up to 18% of hospitalized pediatric patients.[4–6]

While some ADRs are iatrogenic and unpredictable, others are unintended but expected based on the pharmacology of the drug. Regardless of etiology, these ADRs are most likely preventable. In addition to harm, preventable ADRs add unnecessary burden to the patient and caregivers as well as additional cost to the health care system. It has been documented that up to half of ADRs in hospitalized pediatric patients are preventable.[7]

Multiple underlying reasons for higher rates of ADRs in the pediatric population exist, including frequent off-label drug usage, the need for individualized dose

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calculations, and age-related differences in drug disposition and effect. Currently more than 4400 medications are available in the United States, with approximately 50 new medications being approved each year by the US Food and Drug Administration (FDA).[8] The Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA) have stimulated significant research on medications in children.[9] However, 64% of new drugs and biologics lack pediatric prescribing information within 5 years of FDA approval.[10] Additionally, indications for 40% of ordered medications in hospitalized pediatric patients and more than 50% in neonates remain off-label.[11,12] In the outpatient setting, approximately 20% of pediatric and more than 80% of neonatal visits result in 1 or more off-label drug prescriptions.[13] Although lack of FDA labeling does not preclude high-quality, evidence-guided therapy, the high frequency of off-label medication use in the pediatric population is mainly due to the use of older, generic drugs, which did not benefit from the research requirements of PREA and BPCA. The use of many of these older drugs may rely on data from case reports, anecdotal observational experience, and historical dogma to inform prescribing patterns in pediatrics.

An important contributing factor leading to an increased rate of ADRs in the pediatric population is the rapid ontogeny of organs involved in the absorption, metabolism, and elimination of systemic drugs.[14] Specific risk points include a thinner stratum corneum in neonates, enhancing percutaneous absorption of topically administered drugs; immature hepatic enzyme systems in infancy, decreasing metabolism; and incomplete renal glomeruli and tubules for the first year after birth, affecting elimination of drugs and/or metabolites. The complexity and timing of the development of each of these organ systems have the potential to increase ADRs from drugs that have a comparatively lower risk of toxicity in adults.

In the early 1990s, geriatrician Mark Beers led a Delphi study to formulate a list of drugs that are potentially inappropriate for use in patients 65 years and older residing in nursing homes.[15] The "Beers Criteria" have since been updated 6 times, expanded to include all adults older than 65 years, endorsed by the American Geriatrics Society, and integrated into a trademarked software application.[16] The Beers Criteria represent a standard of care that has improved safe prescribing and use of drugs in older adults.[17] A comparable evidence-based list of drugs was published in 2020 that sought to bring a similar focus to unintended and preventable ADRs in the pediatric population, namely the Key Potentially Inappropriate Drugs in Pediatrics, or "KIDs List."[18]

The KIDs List has improved medication safety in pediatric patients through dissemination of evidence-based information, incorporation into information systems, and quality improvement initiatives. Clinician-scientists have used the KIDs List to identify medications associated with a high risk for ADRs at pediatric hospitals and health systems caring for pediatric patients.[19–23] Additionally, the KIDs List has catalyzed vital research in the pediatric population, supporting dialogue among interprofessional practitioners, pediatric institutions, and the public.[24–26] To continue this work, the Pediatric Pharmacy Association (PPA) commissioned an expanded group of pediatric pharmacists to evaluate the medical literature and update the list of drugs that should be "avoided" or "used with caution" in all or a subset of the pediatric population.

Materials and Methods

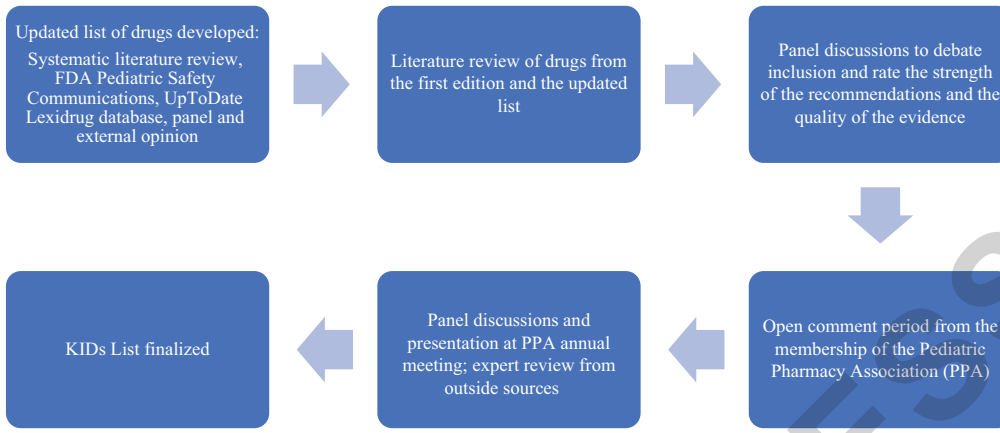
Panel Selection and Composition. The PPA Board of Directors solicited revision of the first edition of the KIDs List on June 20, 2023. All panel members completed a conflict-of-interest disclosure form at the beginning of the process and reaffirmed disclosure at each panel meeting. No panel member had a conflict of interest that precluded participation.

Literature Search and Review. Electronic databases, published communications, FDA product labeling, clinical practice guidelines, panel member expertise, and external reviewers were used to ensure consideration of novel candidate drugs and excipients. The process is described in Figure 1. Published sources were collected, screened, and assessed for eligibility, using the PRISMA strategy.[27]

PubMed. A PubMed search was conducted to identify articles published after data screening for the first KIDs List edition, using a date range of October 1, 2017, to November 1, 2023. The search terms were *adverse drug events* and *adverse drug reactions* as Medical Subject Headings (MeSH) with filters of "English," "Child: birth-18 years," "Humans," and "Case reports," "Observational study," or "Clinical trial." Abstracts were reviewed by 2 panel members. If one of those individuals concluded that the drug or excipient warranted further consideration, the full text was reviewed based on area of subspecialty pediatric expertise and presented to the full panel for consideration.

UpToDate Lexidrug. An UpToDate Lexidrug staff member searched the Lexi-Drugs and Pediatric and Neonatal Lexi-Drugs databases on February 6, 2024. The fields "Warnings: Additional Pediatric Considerations," "Adverse Drug Reaction (Significant) Considerations," "Warnings/Precautions," "Special Alerts List," and "Alert: U.S. Boxed Warnings" were searched by using the following terms: "children" OR "pediatric" OR "neonate" OR "infant" OR "child" OR "adolescent." Two panel members narrowed the list as described in Supplemental Material 1. The list of potential candidate monographs was reviewed by the entire panel with literature searches conducted at the request of any member. Each literature search was conducted by a single panel member, based on area of subspecialty pediatric expertise and presented to the full panel for consideration.

Figure 1. Methods for development of the updated KIDs list.



FDA, US Food and Drug Administration; PPA, Pediatric Pharmacy Association.

FDA Communications. FDA Pediatric Safety Communications (https://www.fda.gov/science-research/pediatrics/fda-pediatric-safety-communications) were searched by 1 panel member. Communications released between January 2019 and March 2024 were reviewed for relevancy for inclusion in the KIDs List.

Anecdotal Observation. Panel members suggested drugs and excipients that were thought to be potentially harmful in pediatric patients. Additionally, the original panel members compiled emails from colleagues regarding exclusions from the first edition. A PubMed search was conducted on each drug. A summary of available evidence was prepared by 2 panelists chosen on the basis of area of subspecialty pediatric expertise. Summaries were reviewed by the full panel.

First-Edition Drugs and Excipients. A PubMed search on each drug was conducted and a summary of available evidence was prepared by 2 panelists chosen on the basis of area of subspecialty pediatric expertise. Summaries were reviewed by the full panel.

External Review. The draft tables were submitted to the members of PPA for review via an electronic communication. Comments were accepted from February 7, 2025, through March 7, 2025. The panel researched all comments for discussion, consensus, and revision to the manuscript, if appropriate.

Operational Definitions. *ADR.* The panel adopted the World Health Organization (WHO) description of an ADR as "a response to a medicine which is noxious and unintended, and which occurs at doses normally used in man."[28]

Potentially Inappropriate Medication. Potentially inappropriate medications were defined as "medications or medication classes that should generally be avoided in persons 18 years or younger because they pose a higher risk of one or more significant ADRs for children than adults and a safer alternative is available." This list is meant to serve as a clinical tool and is not meant to replace clinical judgment or be used in a punitive manner. Needs of an individual patient, disease(s) management, or unique situations may outweigh the recommendations found in this list. The choice of appropriate medications for pediatric patients should be made by an interprofessional health care team, should include individualized dosing and appropriate monitoring, and should consider the values and preferences of the child and caregivers.

Recommendation (Avoid Versus Caution). Two recommendations were used: avoid and caution. Avoid was used when the authors deemed that evidence of clinical benefit did not outweigh the potential adverse effect based on any of the following: the severity of the adverse effect, the quality of evidence supporting clinical utility, and/or the presence of alternative therapies. Caution was used to describe drugs in which benefit in specific clinical scenarios may warrant use despite evidence demonstrating a higher risk of adverse effect(s) in children than adults.

Strength of Recommendation (Strong or Weak). This assessment reflected a classification by the panel describing the seriousness of an ADR, the extent to which the clinician can confidently conclude that the undesirable effect(s) of the intervention outweighs the desirable effect(s). A "strong" recommendation is predicated on the belief that most informed clinicians would choose the recommended course of action. A strong recommendation implies that a clinician presented with information about a specific ADR would choose to avoid or use the drug cautiously in lieu of assuming the risk of the ADR. A strong recommendation allows clinicians to have confidence in their interactions with patients and to structure discussions accordingly. Conversely, a weak recommendation is

consistent with significant variability in the clinician's decision when presented with information about a specific ADR. The clinician must carefully examine specific treatment decisions in this context because these decisions may vary according to the caregivers' and patients' values and preferences.

Quality of Evidence. The quality of evidence reflects the aggregate of published information. The quality of evidence definitions used for the "KIDs List: Second Edition" were based on those from the GRADE recommendations and the Beers Criteria.[29,30] An assessment of "high" quality indicates that further published information or research is very unlikely to alter our confidence in the recommendation or estimate of ADR effect. "Moderate" quality suggests that further research may have a significant impact on our confidence because it may influence or change the evidence regarding a recommendation. "Low" quality implies that further published information or research is likely to affect our confidence in the estimate of effect and may change the conclusion. The KIDs List panel elected to use a "very low" classification of evidence given the paucity of high-quality data on ADRs in pediatrics. "Very low" quality implies that any estimate of effect is very uncertain.

Scope. This list should serve as a useful resource for clinicians and institutions caring for pediatric patients and provide a basis for allocation of resources and additional research to improve drug safety in the pediatric population. During the review process, only those drugs approved for use in the United States, regardless of FDA-labeled age, were considered. Hence, application of this list for pediatric patients in countries other than the United States may be incomplete. It should be noted that some drugs included on this list are also on the WHO Model List of Essential Medicines for Children.[31] Acceptable therapeutic alternatives readily available in the United States (for the same indication) played a role in the expert panel's determination to include a drug in the KIDs List. The KIDs List is not intended to supersede recommendations for drugs found in the WHO Model List of Essential Medicines for Children. Use of these drugs outside the United States for certain clinical conditions may be warranted.

Intent and Audience. The intent of the KIDs List is to improve the safety of medication use in pediatric patients, educate clinicians, and serve as a quality improvement tool. The primary target audience of this publication is health care professionals caring for patients 18 years of age or younger regardless of setting. The KIDs List is intended to be an evidence-based guide to supplement clinical decision-making. The recommendations do not suggest absolute contraindication of any drug in any pediatric patient. As in all medical cases, the entire clinical picture of the patient must be assessed and evaluated by the health care professionals directly involved in the patient's care. Treatment with drugs on this list may be warranted depending on the clinical situation. The KIDs List is not a substitute for clinical judgment. There may be specific populations or diseases for which treatment with any of these drugs is warranted.

Results

Between September 2023 and October 2024, the panel held monthly virtual meetings; live meetings occurred on May 2 and May 3, 2024. A summary of the systematic review and identification of included drugs and excipients is outlined in Figure 2. The initial PubMed search yielded 917 unique titles. Panel members identified 17 articles for full-text review. A search of all 4149 drugs included in the 2 UpToDate Lexidrug databases yielded 1470 unique drugs of which 145 were included for consideration by the full panel (Supplemental Material 1). No relevant FDA Pediatric Safety Communications from the period since the original KIDs List were identified. Twenty-five drugs or drug classes were evaluated on the basis of anecdotal observation. Sixty-seven drugs and/or drug classes and 10 excipients were evaluated on the basis of their inclusion in the first edition.

The final KIDs List contains 39 drugs or drug classes (Table 1). There was sufficient evidence to classify 18 drugs/drug classes as "avoid" in all or a subgroup of pediatric patients; 19 are classified as "use with caution"; 2 drugs were included owing to dosing or concentration limits specific to pediatric patients. Sixty-seven percent of drugs classified as "avoid" had a combination of strength of recommendation plus quality of evidence as either "strong" and "high" or "strong" and "moderate."

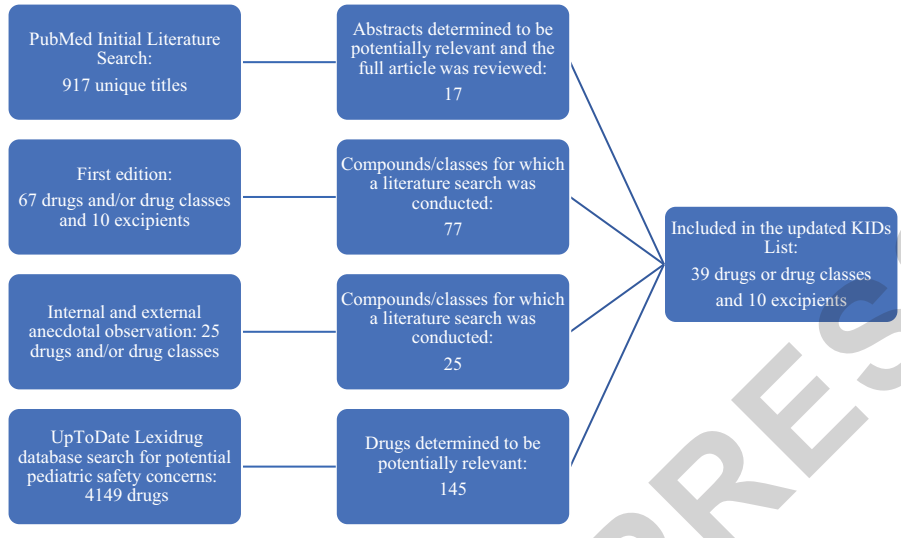
Drugs removed from or added to the KIDs List are outlined in Supplemental Material 2. Among the 5 drugs removed from the list, 3 were removed owing to lack of commercial availability in the United States, while 2 were removed owing to emerging evidence. All drugs added to the KIDs List occurred in the setting of low or very low quality of evidence, primarily consisting of product labeling.

Ten excipients were identified (Table 2). All 4 "avoid" recommendations were conditional, with 3 as dose limitations and 1 contingent upon newborn genetic screening. Moderate- or high-quality evidence drove most recommendations (70%).

Discussion

Lack of an updated evidence-based reference prompted the first edition of the KIDs List.[18] The current publication is an update of the list of potentially inappropriate drugs in pediatrics, reflecting the most current information. Refining the initial process and expanding the author panel led to a carefully compiled list of 39 drugs or drug classes and 10 excipients warranting avoidance or caution in some or all pediatric patients. Notably, these figures represent relative

Figure 2. Results of literature search, expert opinions, FDA Pediatric Safety Communications, and UpToDate Lexidrug database search.



FDA, US Food and Drug Administration.

equilibrium with the first edition, with specific attention paid to highlighting class effects, when supported by evidence. Several debates occurred during roughly 20 hours of panel meetings to produce simple, concise, consensus recommendations, ranging from ancient debates about tetracyclines and teeth to emerging controversies regarding the safety and efficacy of neuropsychiatric medications in children. We have highlighted the rationale behind some of the committee's recommendations below.

Tetracyclines. The impact of tetracycline on teeth has been acknowledged for well over 60 years.[32] Emerging evidence since the first publication of the KIDs List allowed a closer examination of the tetracycline antibiotics as a class. A strong recommendation is now being made to caution against the use of several additional tetracyclines owing to tooth discoloration. It is likely that additional research will further inform the strength of this recommendation. While tetracyclines are known to bind to calcium and are incorporated into teeth and bone to some extent with bone remodeling in persons of all ages, tooth discoloration is most prominent when tetracyclines are administered before mineralization of the succedaneous teeth is completed by 8 years of age, excluding third molars.[33] Although tetracyclines should be avoided in children younger than 8 years, their use may be necessary in some children. Of note, while doxycycline has a similar molecular structure to tetracycline, *in vivo* reports of tooth discoloration, enamel hypoplasia, and bone growth retardation are largely lacking. Therefore, its use in young children is recommended as first-line for the short-term treatment (21 days or less) of susceptible infections, such as rickettsial disease, Lyme disease, vibriosis, and anthrax, where equally effective alternatives are not available.[34]

Antipsychotics. Pediatric mental health has strained the global health system with many clinical considerations informing the use of antipsychotics in youth.[35] Youth are at an increased risk for acute dystonic reactions and hyperprolactinemia with the use of first-generation antipsychotics (e.g., haloperidol) given sensitivity to their potent D_2 blockade within the nigrostriatal and tuberoinfundibular dopamine pathways.[36–40] While first-generation antipsychotics are sometimes used in clinical practice, particularly for the management of acute agitation or aggression, the panel agreed that alternative agents (e.g., olanzapine) are available with a reduced risk for adverse effects. This recommendation is in alignment with updated pediatric treatment guidelines and literature.[41–43]

While second-generation antipsychotics are a reasonable alternative to first-generation antipsychotics in some instances, the panel also considered their many pediatric-specific adverse effects. Metabolic risk is of critical importance in this age group, considering that youth are at an increased risk for developing weight gain, metabolic syndrome, dyslipidemia, and/or type 2 diabetes with second-generation antipsychotic use.[44] The panel acknowledged that their long-term use cannot be avoided in youth with a severe mental illness (i.e., schizophrenia spectrum, bipolar mood disorders), but there are many evidence-based medication alternatives for other indications (e.g., stimulants for impulsive aggression in the setting of attention-deficit/hyperactivity

Table 1. Key Potentially Inappropriate Drugs in Pediatrics (KIDs) List: Second Edition

Drug (Systemic Administration Unless Otherwise Noted)	Risk/Rationale	Recommendation	Strength of Recommendation	Quality of Evidence
Angiotensin receptor blockers[66–69] Azilsartan Candesartan Irbesartan Losartan Olmesartan Telmisartan Valsartan	Renal tubular dysgenesis	Caution in younger than 1 mo	Weak	Very low
Atazanavir[70,71]	Kernicterus	Caution in younger than 3 mo unless pharmacogenetic testing is used	Weak	Very low
Camphor, topical[72–74]	Seizures	Caution in 18 yr of age and younger	Weak	Very low
Carbinoxamine[75]	Death	Avoid in younger than 2 yr	Strong	Low
Ceftriaxone[76–79]	Kernicterus	Caution in younger than 3 wk except for one-time doses for gonococcal treatment	Weak	Very low
Chloramphenicol[80]	Gray baby syndrome	Avoid in younger than 1 mo unless serum concentration monitoring is used	Strong	High
Chlorhexidine, topical[81–83]	Chemical burn	Caution with concentrations >0.5% in less than 7 days old and less than 34 weeks' gestation Caution with concentrations ≥2% in younger than 1 mo	Weak	Low
Corticosteroids, topical (medium, high, and very high potency)[84]	Cushing syndrome, adrenal suppression	Avoid in younger than 2 yr for diaper dermatitis	Strong	Low
Darunavir[85]	Seizures, death	Avoid in younger than 3 yr or ≤10 kg	Strong	Very low
Dicloxacillin[86]	Kernicterus	Caution in younger than 1 mo	Weak	Very low
Dicyclomine[87,88]	Apnea	Avoid in younger than 6 mo	Strong	Low
Difluprednate[89,90]	Increased intraocular pressure	Caution in 18 yr of age and younger	Weak	Low

(Table cont. on page 7)

Table 1. Key Potentially Inappropriate Drugs in Pediatrics (KIDs) List: Second Edition *(cont.)*

Drug (Systemic Administration Unless Otherwise Noted)	Risk/Rationale	Recommendation	Strength of Recommendation	Quality of Evidence
Diphenoxylate and atropine[91,92]	Respiratory failure, death	Avoid in younger than 6 yr	Strong	Moderate
Dopamine antagonists				
First-generation antipsychotics[36–40] Chlorpromazine Droperidol Fluphenazine Haloperidol Loxapine Perphenazine Pimozide Thiothixene Thioridazine Trifluoperazine	Acute dystonic reactions (e.g., oculogyric crisis, torticollis)	Avoid in 18 yr of age and younger	Strong	High
	Hyperprolactinemia		Weak	High
Prochlorperazine[93–95]	Acute dystonic reactions (e.g., oculogyric crisis, torticollis)	Avoid in younger than 2 yr Caution in 2–18 years of age	Strong	Moderate
Second-generation antipsychotics[36,37,44,46,47] Aripiprazole Asenapine Brexpiprazole Cariprazine Clozapine Iloperidone Lurasidone Lumateperone Olanzapine Paliperidone Quetiapine Risperidone Ziprasidone	Withdrawal emergent dystonia/ dyskinesia	Avoid rapid discontinuation in 18 yr of age and younger	Strong	High
	Type 2 diabetes, weight gain, dyslipidemia, and/or metabolic syndrome (risk greater for clozapine ≥ olanzapine > quetiapine > risperidone, paliperidone, iloperidone > asenapine > aripiprazole, brexpiprazole > lurasidone, cariprazine > ziprasidone, lumateperone)	Avoid use of olanzapine for a duration of >12 wk in 18 yr of age and younger Caution in 18 yr of age and younger	Strong	High
	Hyperprolactinemia (risk greater for paliperidone > risperidone > olanzapine)	Caution in 18 yr of age and younger	Strong	High
Metoclopramide[93,96,97]	Acute dystonic reactions (e.g., oculogyric crisis, torticollis)	Avoid in younger than 1 yr Caution in 1–18 yr of age	Strong	High

(Table cont. on page 8)

Table 1. Key Potentially Inappropriate Drugs in Pediatrics (KIDs) List: Second Edition *(cont.)*

Drug (Systemic Administration Unless Otherwise Noted)	Risk/Rationale	Recommendation	Strength of Recommendation	Quality of Evidence
Promethazine[98,99]	Respiratory failure, death Acute dystonic reactions (e.g., oculogyric crisis, torticollis)	Avoid in younger than 2 yr Caution in 2–18 yr of age	Strong	Moderate
Trimethobenzamide[100,101]	Acute dystonic reactions (e.g., oculogyric crisis, torticollis)	Avoid in 18 yr of age and younger	Strong	Low
Ester local anesthetics				
Benzocaine, topical[102]	Methemoglobinemia	Avoid oral application in younger than 2 yr	Strong	High
Lidocaine viscous, topical[103,104]	Central nervous system depression, seizures, arrhythmia, death	Avoid oral application in younger than 2 yr	Strong	High
Gentamicin ophthalmic ointment[105–107]	Severe ocular reactions	Avoid in younger than 1 mo	Strong	High
Guanylate cyclase-C agonists				
Linaclotide[108]	Death from dehydration	Caution in younger than 2 yr	Weak	Very low
Plecanatide[109]	Death from dehydration	Caution in 18 yr of age and younger	Weak	Very low
Lamotrigine[37,110,111]	Skin rashes ranging in severity from benign to life-threatening	Caution in 18 yr of age and younger; slow dose titration required	Strong	High
Loperamide[112]	Ileus, lethargy	Avoid in younger than 3 yr for acute infectious diarrhea	Strong	High
Macrolides[34,113–115] Azithromycin Erythromycin	Hypertrophic pyloric stenosis (risk greater for erythromycin > azithromycin)	Avoid in younger than 1 mo except for *Bordetella pertussis* (azithromycin) or *Chlamydia trachomatis* pneumonia (azithromycin and erythromycin). Caution in younger than 1 mo for *Ureaplasma* (azithromycin).	Strong	High

(Table cont. on page 9)

Table 1. Key Potentially Inappropriate Drugs in Pediatrics (KIDs) List: Second Edition *(cont.)*

Drug (Systemic Administration Unless Otherwise Noted)	Risk/Rationale	Recommendation	Strength of Recommendation	Quality of Evidence
Malathion, topical[116,117]	Organophosphate poisoning	Caution in younger than 2 yr	Weak	Very low
Midazolam[118,119]	Severe intraventricular hemorrhage, periventricular leukomalacia, or death	Caution in patients weighing less than 1500 g	Weak	Low
Mineral oil[120]	Lipid pneumonitis	Avoid in younger than 1 yr	Strong	Low
Mirabegron[121]	Increased blood pressure	Caution in younger than 3 yr	Weak	Very low
Molnupiravir[122]	Bone and cartilage toxicity	Caution in 18 yr of age and younger	Weak	Very low
Montelukast[123]	Sleep disturbances	Caution in 18 yr of age and younger	Weak	Very low
Naloxone[124]	Seizures	Avoid in neonates for postpartum resuscitation	Strong	High
Nitrofurantoin[125]	Hemolytic anemia	Avoid in younger than 1 mo	Weak	Very low
Opioids				
Codeine[126–130]	Respiratory failure, death	Avoid in younger than 12 yr Avoid in 12–18 yr of age after surgery to remove tonsils and/or adenoids Caution in 12–18 yr of age Recommend pharmacogenetic testing	Strong	High
Meperidine[131,132]	Acute neurotoxicity (agitation, myoclonus, hyperreflexia, tremors, delirium, seizures)	Avoid in younger than 1 mo Caution in 18 yr of age and younger	Strong	High
Opium tincture[133]	Respiratory failure	Avoid in younger than 1 mo Caution in 18 yr of age and younger	Weak	Low

(Table cont. on page 10)

Table 1. Key Potentially Inappropriate Drugs in Pediatrics (KIDs) List: Second Edition *(cont.)*

Drug (Systemic Administration Unless Otherwise Noted)	Risk/Rationale	Recommendation	Strength of Recommendation	Quality of Evidence
Tramadol[129,130,134]	Respiratory failure, death	Avoid in younger than 12 yr Avoid in 12–18 yr of age after surgery to remove tonsils and/or adenoids Caution in 12–18 yr of age Recommend pharmacogenetic testing	Weak	Low
Propofol[135–137]	Propofol-related infusion syndrome	Avoid doses >4 mg/kg/hr for greater than 48 hr in 18 yr of age and younger	Strong	Moderate
Ribavirin (oral inhalation)[138]	Sudden respiratory deterioration	Caution in younger than 2 yr	Strong	Low
Salicylates[139,140] Aspirin Bismuth Subsalicylate Salicylic Acid (topical) Salsalate	Reye syndrome	Caution in 18 yr of age and younger with suspicion of viral illness (influenza and varicella)	Weak	Very low
Sodium phosphate solution enema, rectal[141,142]	Electrolyte abnormalities, acute kidney injury, arrhythmia, death	Avoid in younger than 2 yr	Strong	High
Sodium polystyrene sulfonate[143,144]	Colonic perforation	Caution in patients weighing less than 1500 g	Weak	Low
Sulfonamides[145] Silver sulfadiazine, topical Sulfadiazine Sulfamethoxazole	Kernicterus	Caution in younger than 1 mo	Weak	Very low

(Table cont. on page 11)

disorder). While metabolic risk is a class effect, it is important to acknowledge that olanzapine is the only agent that has a manufacturer-specific recommendation to avoid its use first-line in youth given its high risk for metabolic adverse effects.[45] When clinically necessary to use a second-generation antipsychotic, agents with a lower metabolic risk should be considered (see Table 1 for risk delineation). Withdrawal-emergent dystonia/dyskinesia and hyperprolactinemia were also included as important considerations with second-generation antipsychotics, based on updated literature to support pediatric-specific risk.[36,37,44,46,47]

Montelukast. An enhanced focus on pediatric mental health has contributed to novel concerns regarding widely used medications. Montelukast has played a prominent role in the treatment of asthma and allergic conditions in children since its approval in 1998. In 2020, the FDA released a boxed warning about serious neuropsychiatric adverse effects with montelukast.[48] These effects include irritability, aggression,

Table 1. Key Potentially Inappropriate Drugs in Pediatrics (KIDs) List: Second Edition *(cont.)*

Drug (Systemic Administration Unless Otherwise Noted)	Risk/Rationale	Recommendation	Strength of Recommendation	Quality of Evidence
Tetracyclines[33,146–150] Demeclocycline Eravacycline Minocycline Omadacycline Sarecycline Tetracycline Tigecycline	Tooth discoloration	Caution in younger than 8 yr	Strong	High (demeclocycline, tetracycline) Low (minocycline, sarecycline, tigecycline) Very low (eravacycline, omadacycline)
	Enamel hypoplasia (tetracycline)	Caution in younger than 8 yr	Strong	High
	Retardation of skeletal development and bone growth (tetracycline)	Caution in younger than 1 mo	Strong	Moderate
Tricyclic antidepressants[37,151–153] Desipramine Imipramine	Sudden cardiac death	Avoid in 18 yr of age and younger	Strong	High (desipramine) Moderate (imipramine)
Valproic acid and derivatives[37,154–156]	Pancreatitis, fatal hepatotoxicity	Avoid in younger than 2 yr Caution in 2–6 yr	Strong	High
Verapamil[157–159]	Cardiovascular collapse	Caution in younger than 1 yr	Weak	Low

anxiety, and mood disorders and have been reported in both adults and children with similar frequencies. Sleep disturbances such as nightmares have been shown to occur more commonly in children.[49–52] Thus, the KIDs List recommendation is to use caution in children 18 years and younger. While the level of evidence for this recommendation is very low, clinicians should consider the overall risk of neuropsychiatric effects in each individual patient. The KIDs List recommendation is based on the evidence of an increase in sleep disturbances in children. Current evidence does not indicate an overall increased risk in children compared with adults, thus precluding a higher-level warning with montelukast in the KIDs List. Use of montelukast in children should be limited to patients who will benefit and who can be closely monitored for neuropsychiatric effects.

Dopamine Receptor Antagonists. Evidence regarding dopamine receptor antagonists and their therapeutic competitors challenged the authors, given their prevalent adverse effects contrasted against clear therapeutic niches. An increased prevalence or recognition of migraines in pediatric patients has stressed EDs nationwide.[53] Nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, and triptans are guideline-recommended treatment options for pediatric migraines.[54] Emerging literature has suggested that the pathophysiology of pediatric migraines may differ from that of adults.[55] In fact, several studies evaluating triptans for the treatment of pediatric migraine have not demonstrated greater efficacy than placebo. The guidance on medication selection in the ED after NSAIDs, acetaminophen, and/or triptan failure remains limited; however, the development of a standardized migraine protocol that incorporated non-opioid analgesia and a dopamine receptor antagonist was associated with improved patient outcomes.[56] While caution is certainly warranted in pediatric patients, prochlorperazine has demonstrated efficacy for the treatment of acute pediatric migraines; coadministration with diphenhydramine is a reasonable precaution given the risks of developing acute dystonic reactions.[57,58] Metoclopramide may be less effective than prochlorperazine but is a sensible alternative if prochlorperazine is not available or on shortage.[59] Further research is necessary to fully

Table 2. Excipients With Known or Potential Harms When Used in Pediatric Patients

Excipient (Systemic Administration Unless Otherwise Specified)	Rationale	Recommendation	Strength of Recommendation	Quality of Evidence
Benzyl alcohol, sodium benzoate, benzoic acid[63,160,161]	Gasping syndrome	Avoid exposure of >99 mg/kg/day in younger than 1 mo (with the exception of sodium phenylacetate/sodium benzoate used for the treatment of urea cycle disorders)	Strong	High
Ethanol/ethyl alcohol[19,63–65] **(excluding ethanol lock)**	CNS depression, hypoglycemia	Caution in younger than 6 yr: maximum 0.5% v/v ethanol with clinician supervision Caution in younger than 12 yr: maximum of 5% v/v ethanol with clinician supervision	Strong	Moderate
Isopropyl alcohol, topical[162,163]	Chemical burn	Caution in patients weighing less than 1500 g	Weak	Low
Methylparaben, propylparaben[164]	Kernicterus	Caution in younger than 2 mo	Weak	Very low
Phenylalanine[165]	Cognitive and behavioral problems	Avoid in 18 yr of age and younger with an unknown phenylketonuria test	Strong	High
Polysorbate 80[166–168]	Vasculopathic hepatotoxicity (E-Ferol syndrome)	Avoid exposure of ≥72 mg/kg/day in younger than 1 mo Caution exposure of >1.4 mg/day in younger than 1 mo	Strong	High
Propylene glycol[169]	Lactic acidosis, CNS depression, hypoglycemia, hemolysis, seizure	Avoid >1 mg/kg/day in younger than 1 mo Avoid >50 mg/kg/day in 1 mo of age or older to younger than 5 yr	Strong	Moderate

CNS, central nervous system

elucidate the optimal abortive regimen for children presenting to the ED for migraines, particularly after failure of guideline-recommended regimens.

Daptomycin. Important limitations of the KIDs List highlight gaps in knowledge that continue to affect the safety of pharmacotherapy in pediatric patients. As an example, daptomycin was included in the first edition of the KIDs List and subsequently removed in this iteration. The citation in the first edition was the package insert, which continues to state, "Daptomycin for Injection is not recommended in pediatric patients younger than one year of age due to the risk of potential effects on muscular, neuromuscular, and/or nervous systems (either peripheral and/or central) observed in neonatal dogs."[60] The recommendation of caution in the first edition was appropriately classified as weak on the basis of very low-quality evidence. Emerging evidence highlights essential and safe use of daptomycin in infants younger than 1 year.[61,62] Although published evidence represents a small number of infants and ongoing evidence-generation is warranted, human data were given greater weight in our analyses than animal or *in vitro* data. In contrast to daptomycin, many drugs remain on the KIDs List, based on animal or *in vitro* data in the absence of formal human study.

Diphenoxylate/Atropine. Panel members were challenged by clear manufacturer recommendations from product labeling without corresponding supporting data published in peer-reviewed journals. Owing to reported cases of severe respiratory depression and coma, diphenoxylate and atropine should not be administered to patients younger than 2 years. The tablet formulation, specifically, is contraindicated in children younger than 6 years (and recommended for ≥13 years of age). The panel did not change the recommendation from the previous edition and recognizes the challenge for clinicians now that the liquid

product has been discontinued from the market. As more safety data emerge in the pediatric population, the recommendation will be reevaluated. Labeled dosing and warnings will be scrutinized for inclusion and exclusion.

Excipients – Ethanol. Excipients represent a unique challenge to clinicians serving pediatric patients and similarly challenged the authors. Ethanol is commonly used as an excipient to enhance solubility of drugs in solution and prevent microbial growth. Its use in liquid medications for children, both intravenous and oral, has been a cause for concern for decades.[63,64] In 1984, the American Academy of Pediatrics (AAP) published recommendations on limits for alcohol concentrations in over-the-counter medications, and the FDA has similar recommendations published in the Federal Register.[64,65] Despite the recommendations from the AAP and FDA on limits for over-the-counter medications, no recommendations exist for prescription products. In a study published in 2024, seven medications used in pediatric patients were shown to have the potential to increase blood alcohol concentrations above 2.5 mg/dL, which is approximately equivalent to the concentration an adult would experience upon consumption of 10 mL of wine.[19] While the clinical implications of increased blood alcohol concentrations in infants and children remain theoretical, the high concentrations found in some medications for children remain a concern. The current KIDs List recommendation mirrors the limits from the FDA for over-the-counter products, but more data on its risks would help provide clarity on safe limits. Notably, no complete list of drugs containing benzyl alcohol, ethanol, propylene glycol, and other excipients exists. We considered excipients individually and included available information, with a specific focus on thresholds for toxicity. Clinicians must remain diligent in identifying the presence and concentration of these excipients in drugs prescribed to pediatric patients.

Conclusions

An extensive review of primary literature and tertiary references, followed by a robust panel discussion of pediatric pharmacotherapy specialists, facilitated an updated list of drugs and excipients that should generally be avoided or used with caution in all or select subgroups of pediatric patients. The first edition of the KIDs List has served as a valuable tool to improve drug safety for children, functioning as an evidence-based reference of the risks associated with relatively contraindicated drugs in the pediatric population. The list also has served as a reference to combat historical dogma, accurately reflecting the rationale and level of evidence supporting contraindications and highlighting knowledge gaps in the published literature. Recommendations have been revised from the 2020 publication, based on novel research and robust feedback from the community of health care professionals serving pediatric patients. Knowledge of pediatric pharmacology has expanded at an encouraging pace to inform the second edition of the KIDs List. However, significant gaps in knowledge still exist and justify the promotion of both prospective and retrospective safety studies of pediatric pharmacotherapy. This list represents a single step in the ongoing work of clinicians and researchers to continuously improve drug safety for children.

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