Pediatric Health, Medicine and Therapeutics

Dovepress
open access to scientific and medical research

Open Access Full Text Article

REVIEW

Clinical Toxicology of OTC Cough and Cold Pediatric Medications: A Narrative Review

Ajeng Diantini[1,2,*], Mohammed Alfaqeeh[3,*], Lanny Indah Permatasari[3,*], Mirna Nurfitriani[3,*], Lela Durotulailah[3,*], Wening Wulandari[3,*], Truly Deti Rose Sitorus[4], Gofarana Wilar[1,2], Jutti Levita[1,2,*]

[1]Department of Pharmacology and Clinical Pharmacy, Faculty of Pharmacy, Padjadjaran. University, Sumedang, West Java, 45363, Indonesia; [2]Center of Excellence in Higher Education for Pharmaceutical Care Innovation, Padjadjaran University, Sumedang, West Java, 45363, Indonesia; [3]Master Program in Clinical Pharmacy, Faculty of Pharmacy, Padjadjaran University, Sumedang, West Java, 45363, Indonesia; [4]Department of Pharmacology and Therapy, Faculty of Medicine, Padjadjaran University, Sumedang, West Java, 45363, Indonesia

*These authors contributed equally to this work

Correspondence: Jutti Levita, Department of Pharmacology and Clinical Pharmacy, Faculty of Pharmacy, Padjadjaran University, Sumedang, West Java, 46363, Indonesia, Tel +6222-84288888 Ext 3510, Email jutti.levita@unpad.ac.id

Video abstract

Point your SmartPhone at the code above. If you have a QR code reader the video abstract will appear. Or use: https://youtu.be/lSxLamsvaBg

Abstract: Cough and cold symptoms (CCS) are common pediatric conditions often treated with over-the-counter (OTC) medications. However, the available knowledge regarding the safety and toxicity of these medications in children is inadequate. Therefore, understanding their clinical toxicology is crucial for safeguarding children's well-being. This narrative review highlights the importance of clinical toxicology in evaluating the safety and toxicity profile of OTC medications for treating CCS in pediatric patients. The pharmacology, clinical features, and adverse effects of various drug classes commonly found in cough and cold medications are briefly discussed. Pharmacokinetic and pharmacodynamic parameters are also examined to understand the interactions between these drugs and the body. OTC cough and cold medications often contain active ingredients such as antihistamines, decongestants, antitussives, expectorants, and analgesics-antipyretics. The combination of multiple ingredients in these products significantly increases the risk of adverse effects and unintentional overdoses. Several case studies have reported significant toxicity and even fatalities associated with the use of these medications in children. This review underscores the critical importance of clinical toxicology in evaluating the safety and toxicity profile of OTC medications employed for treating CCS in pediatric patients. The findings highlight the significance of informed clinical practice and public health policies to ensure the well-being of children using OTC cough and cold medications.

Keywords: bromhexine, chlorpheniramine maleate, dextromethorphan, glyceryl guaiacolate, paracetamol, pseudoephedrine

Introduction

Cough and cold symptoms (CCS) refer to upper respiratory tract infections commonly characterized by nasal congestion (sometimes accompanied by rhinorrhea), coughing (usually caused by inflammation of the lower respiratory tract), and throat discomfort.[1] CCS are prevalent pediatric conditions,[2,3] causing parents and caregivers to choose over-the-counter (OTC) medications as the solution.[4,5] OTC medications refer to non-prescription drugs that are available without prescription.[6] A cross-sectional study conducted by Slack-Smith et al on the prevalence of medication use among children attending daycare found that 73% of the children had received OTC medications.[7] OTC medications, such as paracetamol,[8] pseudoephedrine,[9] dextromethorphan,[10] chlorpheniramine maleate (CTM),[11] phenylephrine,[12] phenylpropanolamine (PPA),[13] guaifenesin or glyceryl guaiacolate,[14] and bromhexine,[15] are commonly used for CCS treatment with some preparations containing a combination of two or more of these drugs,[16] which can be beneficial when administered properly. The goal of therapy is to reduce symptoms, thus improving the recovery period.[17,18]

Received: 17 April 2024
Accepted: 29 June 2024
Published: 11 July 2024

A study examining 6552 cases described that products containing diphenhydramine and dextromethorphan were associated with the majority of hospital admissions in healthcare facilities. Remarkably, diphenhydramine displayed the highest admission rates and was the sole ingredient to exhibit a consistent increase over time.[19] The yearly revenue for OTC medications in the United States is around $3.5 billion, with a weekly administration of about 4 million children.[20] A study mentioned that of 178 reported deaths, 28% of them were related to OTC medications.[21] OTC medications are marketed under monograph guidelines that do not necessitate pre-market reviews of their ingredients and may include excipients in prescription items, whose formulations differ from those approved through New Drug Applications (NDAs).[22] Moreover, in November 2022, Gambia recorded 70 fatalities among children under the age of five which have been linked to the contaminated anti-histamine and cough-and-cold syrups.[23] Similarly, in Indonesia during the same year, a significant increase in cases of acute kidney injury among children was reported, with 199 deaths due to the contaminated local syrup products containing traces of diethylene glycol (DEG) or ethylene glycol (EG).[23] Therefore, understanding the safety and toxicity profile of these medications is of utmost importance in safeguarding children's well-being.

Clinical toxicology serves as a vital field for assessing the adverse effects of medications and chemicals in humans.[24] Research focusing on pediatric hospital admissions related to poisoning indicates that children under the age of five comprise a substantial majority, accounting for approximately 86% of all child poisoning admissions. The peak incidence of poisoning cases occurs at the age of 2 years.[25] One of the most common poisoning agents was cough and cold medications.[26] Wang et al reported that among the 3134 cases reviewed, 65.9% experienced adverse events resulting from accidental unsupervised ingestions, which were deemed to be, at the very least, potentially associated with a constituent of cough and cold medications.[27] Considering the specific focus on OTC cough and cold medications, clinical toxicology assumes particular importance in assessing their safety in pediatric patients. However, the existing knowledge regarding the clinical toxicology and safety evaluation of these OTC medications is limited.[28]

Children are particularly vulnerable to OTC medication poisoning due to their developing physiology and immature drug metabolism and excretion systems.[29,30] Furthermore, improper or excessive use of OTC medications in pediatrics may lead to significant risks of adverse effects. Wang et al noted that cough and cold medication errors, particularly those containing diphenhydramine and dextromethorphan, were frequently linked with volume miscalculations by the caregiver administration.[31]

Therefore, this review aims to highlight the importance of clinical toxicology in evaluating the safety and toxicity profile of OTC medications for treating CCS in pediatric patients. Additionally, two case studies will be presented to provide a real-world example of a child who experienced adverse effects from OTC cough and cold medications. Furthermore, the importance of clinical toxicology in assessing the safety and toxicity profile of OTC cough and cold medications cannot be overstated, as it provides a valuable framework for understanding the risks and benefits of these medications, informing clinical practice, and shaping public health policy.

Pharmacology

Medication utilization remains prevalent among children aged 0–18 months. According to the study conducted in Indonesia by Thobari et al in 2020, approximately 82.2% of 1621 pediatric patients were using at least one medication during the 18-month follow-up period, including cough and cold medications accounting for 13.5%.[32] Cough and cold medications contain active pharmaceutical ingredients (APIs), that are given as a single component or in combination, and are intended to relieve some or all symptoms.[33] The most common medication used to treat CCS is a combination of several drugs, including CTM (58.8%), paracetamol (56.5%), guaifenesin (50.6%), pseudoephedrine (28.2%), dextromethorphan (22.4%), and bromhexine (9.4%), with a total of approximately 250 brands.[33–35] Of these, about 31.2% (78 brands) are included in the category of *G* (*Gevaarlijk* which means dangerous or harmful) list of drugs. These *G*-category drugs can be authorized with a prescription scribbled by a medical practitioner. The rest (roughly 68.8%) are cough and cold medicine products that fall into the category of OTC drugs.[33–35] The drugs commonly found in many cough and cold medications consist of antihistamines, decongestants, antitussives, expectorants, analgesics-antipyretics, and a combination of these medications.[35]

Antihistamines are compounds that act as antagonists of histamine receptor type H1 (H1R), a member of the superfamily of G-protein-coupled receptors (GPCRs).[36] H1R-antihistamines inhibit H1R on blood vessels in the nose and compete with

histamine to bind to those receptors, thus aiming to overcome symptoms such as sneezing, rhinorrhea, and watery eyes.[35] Some commonly used first-generation antihistamines include CTM, diphenhydramine, mepyramine, and promethazine. However, Cochran's meta-analysis concluded that the use of a single antihistamine was not significant in clinically reducing symptoms of sneezing and rhinorrhea, nor did it provide subjective improvements in either children or adults.[34]

Decongestants are medications that function as stimulants of adrenergic alpha-1 receptors. Pseudoephedrine and ephedrine are examples of decongestants that are often used in various types of cough and cold medications. Decongestants work by reducing mucous membrane secretion and swelling in the nasal passages, effectively relieving nasal congestion and facilitating unobstructed breathing through the nose. However, it is important to note that decongestants can also cause vasoconstriction in other parts of the body. Therefore, the use of decongestants is not recommended in individuals with uncontrolled hypertension, hyperthyroidism, as well as heart diseases.[34]

Antitussives are medications that have a central mechanism of action that involves suppressing the cough center in the medulla part of the brainstem. Codeine and dextromethorphan are commonly used antitussives. However, because of its potential for abuse, codeine is classified as a narcotic drug in Indonesia, although when it is used in antitussive doses, it shows no addictive effects. Dextromethorphan is the D-isomer of levo-phenol,[37] that shows a pharmacological mechanism similar to codeine as an antitussive, but not classified as narcotics. However, when used at high doses, it produces narcotic-like addictive effects.[34]

Expectorants are used to assist in the dissolution of respiratory tract secretions, making them easier to expel. Guaifenesin is the most commonly utilized medication in this category. Additionally, it is the only approved expectorant by the US Food and Drug Administration (FDA).[38] However, guaifenesin lacks substantial scientific support for its efficacy in pediatric populations. The available studies have not demonstrated significant advantages of expectorant use in children.[35]

Analgesics-antipyretics are used to help control fever and relieve pain in general. Ibuprofen and acetaminophen are the most commonly used analgesics and antipyretics. Ibuprofen is classified as a non-steroidal anti-inflammatory drug (NSAID) that works by blocking the catalytic function of cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) enzymes, thus resulting in a decrease of prostaglandin productions. Prostaglandins are known as pro-inflammatory mediators. Another analgesics-antipyretic is acetaminophen which can pass the blood-brain barrier similarly to NSAIDs, allowing it to enter the central nervous system and inhibiting cyclooxygenase-3 (COX-3), thus reducing the generation of pro-inflammatory polypeptides. This may also be the reason why acetaminophen is frequently more successful than some other NSAIDs at treating headaches and fever.[39]

Combinations of the previously discussed OTC cough and cold medications are more often used for treating CCS rather than single ones. Due to the presence of these combinations, symptoms of toxicity are more often associated with the use of these medications. Many combinations have been approved by the Indonesian National Agency of Drug and Food Control. Several combination products for the treatment of cough and cold on the market have varying components of different pharmacological classes (summarized in Table 1).

Clinical Features and Adverse Effects

The primary objective of cough and cold treatment is to provide temporary relief of symptoms while allowing the illness to run its course.[35] However, studies have reported adverse effects associated with the inappropriate use of OTC cough and cold medications. Although most cough and cold medication overdoses are not fatal, reports are showing significant severity and risk of death associated with their use.[14]

Over two-year periods, more than 1500 children under the age of 2 years old were admitted to emergency departments for adverse events associated with the use of OTC cough and cold medications. The risk of overdoses, dosage errors, and adverse events tends to be higher in young children because they have more frequent colds each year.[4] In 2008, OTC cough and cold medications underwent a label change in response to concerns over their safety, including reports of deaths in children exposed to cough and cold medications.[40] It is estimated that there are over 800 OTC cough and cold medications available in the US, and according to surveillance studies, 81.7% of the most common cases involving these medications were in liquid form, with medication errors often occurring due to incorrect liquid volume and formulations of single ingredients, leading to adverse effects.[31,41] The Medicine and Healthcare Products Regulatory Agency (MHRA) in the United Kingdom (UK) and Health Canada both advised against using many cough and cold

Table 1 Combinations of OTC Cough and Cold Medications

Components in OTC Combination	Number of OTC Syrup Products
Antihistamines, decongestants	14
Antihistamines, decongestants, analgesics-antipyretics, antitussives	12
Antihistamines, decongestants, analgesics-antipyretics	8
Antihistamines, analgesics-antipyretics, expectorants	11
Antihistamines, decongestants, antitussives, expectorants	13
Antihistamines, decongestants, analgesics-antipyretics, antihistamines, antitussives, expectorants	6
Antihistamines, decongestants, expectorants	10
Antihistamines, expectorants	9
Antihistamines, decongestants, antitussives	7
Antihistamines, antitussives, expectorants	4
Antihistamines, analgesics-antipyretics, expectorants	2
Antihistamines, antitussives	3
Analgesics-antipyretics, decongestants, antitussives	2
Decongestants, antitussives	2
Decongestants, expectorants	1
Decongestants, antitussives, expectorants	1

medications in children under six years old, Italy issued a warning for nasal sympathomimetics in children under twelve years old in 2007, but no such national warnings were issued in the Netherlands and other countries.[42]

The potentially inappropriate use of these medications in children has led to a significant impact on morbidity and mortality rates. The most common adverse effects of several types of OTC cough and cold medications based on pharmacological classes, namely antihistamines, decongestants, antitussives, analgesics-antipyretics, and expectorants are presented in Table 2.[33]

Table 2 Pharmacological Classes of OTC Cough and Cold Medications and Their Adverse Effects

Pharmacological Classes	Example	Adverse Effects	References
Antihistamines	Brompheniramine, CTM, Diphenhydramine	Increased heart rate, high blood pressure, increased body temperature, redness of the skin, dryness of the mucous membranes, dilated pupils, hallucinations, fatigue, sedative effect, acute psychosis, convulsions	[33]
Decongestants	Phenylephrine	Increased heart rate, high blood pressure, increased body temperature, dilated pupils, anxiety, confusion, convulsions, warm skin with sweat	[33]
Antitussives	Dextromethorphan	Hallucinations, speech disorders, memory impairment, uncontrolled eye movements	[33]
Analgesics-antipyretics	Acetaminophen	Risk of liver damage	[33]
Expectorant	Guaifenesin	Nausea and vomiting	[33]

Abbreviation: CTM, chlor-trimeton or chlorpheniramine maleate.

Individual variances in drug reactions and adverse effects exist, and drug selection is a crucial issue. Although a variety of factors contribute to individual variances in medication response, there is solid evidence that genetic factors play a substantial role in drug response variability and toxicity.[43] Children and adults have different ontogeny and metabolic capacities. Several distinct developmental changes in children may account for the observed variations in drug responsiveness. They can also cause negative medication responses.[44] Drug-drug interactions also affect variances in an individual's response to medications. It is described as a potential relationship between two or more medications that might alter the efficacy and/or toxicity of one or both medications.[45] Some important drug-drug interactions in OTC cough and cold medications that could lead to toxicity can be seen in dextromethorphan with monoamine oxidase inhibitors (MAOIs), eg phenelzine and selegiline, selective serotonin reuptake inhibitors (SSRIs) eg sertraline, fluoxetine, and escitalopram,[46] and in H1R-antihistamines with some antidepressants, anxiolytics, hypnotics, and beta-blockers.[47] When considering factors that may increase the risk of toxicity beyond the inherent properties of a drug, it is important to exercise caution when administering OTC cough and cold medications to children. The factors can vary significantly by location, for example, in some regions, certain medications may be accessible without a prescription, while in others, the same medications may require a prescription due to regulatory controls,[47] therefore, affect the prevalence of adverse effects and toxicity cases.[48] Countries with strict regulations may have lower incidences of medication-related poisoning in children compared to regions with more lenient policies.[49] Understanding these regional differences is essential for developing targeted strategies to improve medication safety and efficacy, and to inform global public health policies.

Pharmacokinetics and Pharmacodynamics

The pharmacokinetic and pharmacodynamic interactions between the drug and the body play an important role in drug therapeutic effects and toxicity. High drug doses or changes in absorption, distribution, metabolism, and excretion may cause toxic effects. The initial amount, route of administration, drug formulation, and bioavailability can directly affect the amount of response to medications. Doses, along with their frequencies, duration of exposure, and pharmacodynamic variabilities, will influence the toxicity in the body.[50] The pharmacokinetic and pharmacodynamic parameters of several components of cough and cold medications are summarized in Table 3.

Toxicokinetics and Toxicodynamics

Toxicokinetics is the quantitative relationship among absorption, distribution, biotransformation, and excretion of toxicants and their metabolites, while toxicodynamics is the molecular, biochemical, and physiological effects of toxicants and their reactive intermediates, or the dynamic interactions of toxicants and their reactive intermediates with biological macromolecules. Toxicants and their reactive intermediates, similar to other xenobiotics, indicate a biological affinity for cellular macromolecules such as proteins, ion channels, DNA, and a wide range of receptors. The identification of cellular macromolecules or receptors that are targeted, as well as the overall toxic effect (toxidromes) at both cellular and organism levels, is contingent upon the mechanism of action and can be inferred from their chemical characteristics. Consequently, an integration of toxicokinetics and toxicodynamics is necessary to assess the potential impacts and harmful mechanisms associated with these substances.[65]

Acetaminophen has a mechanism of toxicity that involves the result of its metabolism that produces the reactive intermediate N-acetyl-p-benzoquinonimine (NAPQI). The majority of acetaminophen metabolism at therapeutic levels takes place via glucuronidation and sulfation to nontoxic metabolites. Acetaminophen metabolism to NAPQI emerges as a significant metabolic pathway in overdose when the nontoxic routes of metabolism become saturated. NAPQI is largely formed through hepatic cytochrome P450 subfamily 2E1 (CYP2E1) oxidation, with minor contributions from CYP3A4, CYP2A6, and CYP1A2. At therapeutic dosages, the hepatic glutathione efficiently neutralizes NAPQI by forming harmless compounds that are excreted as mercapturic acid in the urine. However, in cases of overdose, the production of NAPQI escalates proportionally to the consumed dose. When the rate at which glutathione is produced falls behind its utilization, toxic effects ensue. This glutathione depletion leads to the release of unbound NAPQI, which swiftly binds to hepatocytes, resulting in apoptosis or direct cellular necrosis. The detrimental outcomes stem from the covalent attachment of NAPQI to essential cellular constituents.[66]

Table 3 Pharmacokinetics and Pharmacodynamics of OTC Cough and Cold Drug Components in Pediatrics

Drugs	Pharmacokinetics Process	Pharmacokinetic Parameters		Pharmacodynamics	References
Acetaminophen	Absorption	Bioavailability	~72%	The analgesic effects are thought to be brought on by the activation of descending serotonergic inhibitory pathways in the CNS, while the antipyretic effects result from the inhibition of the hypothalamus heat-regulating center	[51–54]
		pKa	9.38		
	Distribution	Volume distribution	0.85–1.5 L/kg		
		Protein binding	10–30%		
	Metabolism	-	Metabolized in the liver to sulfate and glucuronide conjugates.		
	Excretion	T ½	2.6–2.8 hours		
		Clearance	400 mL/minute		
Pseudoephedrine	Absorption	Bioavailability	N/A	It directly stimulates beta-adrenergic receptors, while indirectly it activates alpha-adrenergic receptors, triggering the release of endogenous norepinephrine from neuronal granules	[55–57]
		pKa	10.25		
	Distribution	Volume distribution	~2.5 L/kg		
		Protein binding	20%		
	Metabolism		Metabolized in the liver to produce active nor-pseudoephedrine (<1%).		
	Excretion	T ½	~3 hours		
		Clearance	7.3–7.6 mL/minute/kg		
Dextromethorphan	Absorption	Bioavailability	11%	It works by reducing the sensitivity of cough receptors and preventing the transmission of cough impulses by suppressing the medullary cough center through the activation of sigma receptors	[51,58–60]
		pKa	9.8		
	Distribution	Volume distribution	5.0–6.7 L/kg		
		Protein binding	60–70%		
	Metabolism	-	Metabolized in the liver to dextrorphan (active) and lower quantities of 3-hydroxy and 3-methoxy derivatives.		
	Excretion	T ½	4.9–6.41 hours		
		Clearance	33.8 mL/minute/ kg		
CTM	Absorption	Bioavailability	59%	It is competing with histamine for H1-receptor sites on effector cells in the respiratory system, gastrointestinal tract, and blood vessels	[61–64]
		pKa	9.2		
	Distribution	Volume distribution	7 L/kg		
		Protein binding	29–37%		
	Metabolism		Metabolized in the liver to active and inactive metabolites.		
	Excretion	T ½	13.1 hours		
		Clearance	N/A		

Abbreviations: CTM, chlor-trimeton or chlorpheniramine maleate; pKa is the acid dissociation constant; T½, half-life of a drug; CNS, central nervous system; N/A, not available.

Pseudoephedrine is a stereoisomer of ephedrine. It has activity towards direct and indirect alpha- and beta-adrenergic systems. Pseudoephedrine causes the release of norepinephrine from neurons and later increases sympathetic tone and stimulates the central nervous system (CNS) by directly stimulating adrenergic receptors. Additionally, it stimulates the beta-adrenergic system more than PPA or phenylephrine does.[67] Activation of alpha-adrenergic receptors by pseudoephedrine leads to vasoconstriction, potentially increasing blood pressure and reducing blood flow in certain vascular beds. Furthermore, its beta-adrenergic receptor activation induces bronchodilation, increased heart rate, and enhanced heart contractility.

Dextromethorphan is biotransformed to its active metabolite dextrorphan by CYP2D6. Dextrorphan is likely to be responsible for any adverse effects that may occur. Dextromethorphan and dextrorphan are N-methyl-D-aspartate (NMDA) glutamate receptor antagonists. However, dextrorphan has a stronger effect and is mostly in charge of high doses of dextromethorphan's euphoric side effects. The varying clinical reactions may be due to CYP2D6 genetic variation; extensive metabolizers are more likely to experience the "desirable" euphoric effects with recreational usage. Particularly in individuals taking medications that raise serotonin levels, such as MAO-Is and SSRIs, dextromethorphan and dextrorphan impede the reuptake of serotonin and may cause serotonin syndrome. Dextromethorphan's potential for misuse in both the acute and chronic phases may be explained by serotoninergic effects as well as NMDA glutamate receptor inhibition.[67]

Diphenhydramine and CTM exert anticholinergic effects and may also stimulate or depress the CNS, and may affect learning and examination performance in children.[49] Therefore, overdose may cause symptoms similar to those of anticholinergic poisoning. The hepatic CYP450 system is responsible for the metabolism of all first-generation H1R-antihistamines. Therefore, these medications can have an impact on the plasma concentrations of H1R-antihistamines, either toxic or decreasing their action. The concurrent administration of H1R-antihistamines with alcohol, opioid analgesics, anxiolytics, and hypnotics may lead to increased sedation, potentially exacerbating sedative effects. In combination with tricyclic and MAOI antidepressants, H1R-antihistamines may produce enhanced antimuscarinic effects. Furthermore, the concomitant use of beta-blockers and antiarrhythmics with H1R-antihistamines may elevate the risk of ventricular arrhythmias. Compared to first-generation H1R-antihistamines, second-generation ones offer a wider safety margin, thereby reducing the occurrence of sedative interactions. Consequently, interactions are generally less likely to cause significant side effects. As a result, interactions are generally less likely to result in major side effects.[68] The usual daily pediatric dose, toxic dose, and potential toxidromes of acetaminophen, pseudoephedrine, dextromethorphan, and CTM are presented in Table 4.

Case Report 1

A case report in Türkiye of a 3-year-old boy with abdominal pain and difficulty urinating for the past 12 hours. The boy was admitted to the emergency department. No additional symptoms, such as nausea, vomiting, or constipation, were reported alongside the provided information. The medical history revealed that the pediatric patient had experienced a common cold 10 days prior and had been given pseudoephedrine hydrochloride at a dosage of 90 mg per day, divided into three doses, without consulting a medical practitioner. Upon admission to the emergency department, the patient's weight was recorded as 11 kg, and his height was measured at 92 cm. The examination showed a body temperature of 37°C, a heart rate of 110 beats per minute, and blood pressure of 100/60 mmHg. Moreover, there was an abnormal suprapubic mass as a result of external genital examination. There were no signs of abdominal tenderness, rebound, or defense. A urinary catheterization successfully drained 750 mL of urine. Laboratory evaluations, including complete blood count, liver and kidney function tests, and urinalysis, reported results within normal limits. The radiological evaluation indicated a normal lumbosacral graph. There was no hydronephrosis or urethral dilation on kidney ultrasonography. The patient was diagnosed with acute urinary retention due to an excessive dose of pseudoephedrine. A urology examination and discontinuation of pseudoephedrine consumption were planned. No other signs of pseudoephedrine overdose were found, especially during cardiac and neurological examinations. Twelve hours after the last dose of pseudoephedrine, the difficulty in urination was resolved, and the patient was discharged from the hospital.[69]

Table 4 Summary of the Usual Daily Pediatric Dose, Toxic Dose, and Potential Toxidromes of OTC Cough and Cold Medications

Drugs	Usual Daily Pediatric Dose	Toxic Dose	Toxidromes (Toxicity Syndromes)	References
Acetaminophen	10 to 15 mg/kg/dose every 4 to 6 hours as needed; do not exceed 5 doses in 24 hours; maximum daily dose: 75 mg/kg/day not to exceed 4,000 mg/day.	Hepatotoxicity potentially occurs with acute ingestion of more than 200 mg/kg. According to the American Association of Poison Control Centers (AAPCC) guideline, ingestion of doses higher than 150 mg/kg/day for 2 days or 100 mg/kg/day for 3 days needs medical evaluation.	Acute overdose: anorexia, nausea, vomiting, altered mental status, hypotension, and metabolic acidosis. Massive overdose within 24–48 hours: hepatic necrosis with increased aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels, accompanied by encephalopathy, metabolic acidosis, elevated PT/INR, and acute renal failure. Chronic excessive: nausea, vomiting, hepatic injury, and depletion of glutathione, resulting in anion gap metabolic acidosis.	[43,46,51–54,66]
Pseudoephedrine	3–5 mg/kg	Toxidromes start to appear 4–5 times the average therapeutic dose.	Effects on the cardiovascular system: tachycardia, hypertension, dysrhythmias, and myocardial infarction. Effects on CNS: agitation, psychosis, paranoia, hallucinations, seizure, and intracranial hemorrhage	[43,55–57]
Dextromethorphan	2 to <6 years: 5 mg every 4 h as needed; max. 6 doses in 24 hours	A dose more than 10 mg/kg usually causes moderate symptoms.	Effects on CNS: ataxia, somnolence, mydriasis, tachycardia, and hallucinations. General effects: flushing, rash, and respiratory symptoms such as hypoxia, respiratory depression, apnea, decreased respiratory rate, hypopnea, hypoventilation, respiratory disturbance, and respiratory failure, are also results of the toxicity of dextromethorphan	[43,51,58–60]
	6 to <12 years: 10 mg every 4 h as needed; max. 6 doses in 24 hours			
	12 to 18 years: 20 mg every 4 h as needed; max. 6 doses in 24 hours			
CTM	2 to <6 years: 1 mg every 4–6 h, max. 6 mg daily	The lethal dose of antihistamines in children may be as low as 20–30 pills, and toddler deaths and major poisonings have been linked to doses of 10–60 mg/kg.	Drowsiness, dilated pupils, flushed dry skin, fever, tachycardia, delirium, hallucinations, myoclonic movements, and serious overdose may result in convulsions, rhabdomyolysis, and hyperthermia	[43,61–64]
	6 to <12 years: 2 mg every 4–6 h, max. 12 mg daily			
	12 to 18 years: 4 mg every 4–6 h, max. 24 mg daily			

Case Report 2

In another case, a 2-year-old boy weighing 10.8 kg without a prior serious medical history was drawn to the emergency department for walking like a drunk. The child experienced upper respiratory disorders for the previous 2 days and received three doses of one and a half teaspoons of a cough drug, which contains pseudoephedrine 15 mg and dextromethorphan 7.5 mg in 5 mL, 6 hours before being taken to the hospital. The last dose was given 3 hours before the symptoms appeared, after which the child slept for 1 hour but woke up in a state of hyperexcitability, rapid anger, inconsistent choking, and difficulty keeping balance. Based on the findings of the physical examination, the patient exhibited hyperactivity, ataxia, reactive pupil dilation measuring 4 mm, and early tachycardia with a heart rate of 180 beats per minute. The result of the electrocardiograph after 30 minutes of being at the emergency department showed a heart rate of 130 times per minute without evidence of ischemia or dysrhythmia and systolic blood pressure of 100 mmHg. In addition, the child's speech has begun to return to normal, but ataxia and hyperactivity remain. The results of the computed tomography scan of the head and the urine analysis were normal. In the toxicological examination of the blood after 3.5 hours of the last dose were obtained serum dextromethorphan 240×10^{-6} μg/mL and pseudoephedrine 2.2×10^{-3} μg/mL. The condition of the patient returned to normal after observation for 4 hours at the ED, and he was returned home.[70]

The Impact of Dose on Toxicokinetics and Toxicodynamics

In the first case, it was reported that the patient had previously taken pseudoephedrine at a dose of 90 mg/day.[69] The daily dose of pseudoephedrine for children is 3–5 mg/kg, thus the daily dose for a child weighing 11 kg should be in the range of 33–55 mg/day.[69,71] Pseudoephedrine is utilized to treat the symptoms of nasal and sinus congestions associated with seasonal rhinitis and the common cold. It is considered to be relatively less toxic, as symptoms typically manifest after four to five times the usual therapeutic dose. The main toxic effect of this drug is hypertension, which can cause headaches, confusion, seizures, and intracranial hemorrhage. Urinary retention is also one of the side effects of pseudoephedrine which is attributed to the relaxation of the detrusor muscle of the bladder (via the activation of β3-adrenoreceptors in the bladder) and the simultaneous contraction of both the internal urethral sphincters and external urethral sphincters (via stimulation of α1-adrenoreceptors in the bladder).[71]

In the second case, the patient was given a combination of pseudoephedrine and dextromethorphan in the syrup dosage form.[70] The dose of dextromethorphan for children aged 2 to < 6 years is 5 mg every 4 hours; if a maximum dose is needed, then it is given 6 times in 24 hours. Doses greater than 10 mg/kg usually cause moderate symptoms.[67,72] Dextromethorphan was developed as a CNS antitussive agent with a mechanism of reducing cough receptor sensitivity and preventing the transmission of cough impulses by suppressing the medullary cough center through sigma receptor activation, structurally similar to codeine.[72]

Acute urinary retention is very rare in childhood. In a study conducted by Gatti et al in 2001, a total of 53 cases of acute urinary retention in children were reported. The etiological factors identified in these cases included neurological processes (17%), severe voiding dysfunction (15%), urinary tract infection (13%), constipation (13%), local inflammatory causes (7%), locally invaded neoplasms (6%), benign obstructive lesions (6%), and incarcerated inguinal hernias (2%). Adverse drug events accounted for 13% of all cases and were found to be three times more prevalent in males.[73]

Overdosage of dextromethorphan in pediatrics has been reported to cause mild symptoms, and some cases are considered not life-threatening. However, several recommendations for dextromethorphan poisoning are as follows: 1) All patients with suicidal intent, intentional abuse, or in cases in which malicious intent is suspected (eg, child abuse or neglect) should be referred to an emergency department; 2) Patients who exhibit more than mild effects after acute dextromethorphan ingestion should be referred to an emergency department; 3) Patients who have ingested 5–7.5 mg/kg should receive poison center-initiated follow-up approximately every 2 hours for up to 4 hours after ingestion; 4) Patients who ingested > 7.5 mg/kg should be referred to an emergency department for evaluation; 5) If the patient is taking other medications likely to interact with dextromethorphan and cause serotonin syndromes, such as MAOIs or SSRIs, poison center-initiated follow-up every 2 hours for 8 hours is recommended; 6) Patients who are asymptomatic and more than 4 hours have elapsed since the time of ingestion can be observed at home; 7) Do not induce emesis; 8) Do not use activated charcoal at home; 9) For patients who have ingested dextromethorphan and are sedated or comatose, naloxone, in the

usual doses for treatment of opioid overdose, can be considered for prehospital administration, particularly if the patient has respiratory depression; 10) Use intravenous benzodiazepines for seizures and benzodiazepines and external cooling measures for hyperthermia; 11) Carefully ascertain by history whether other drugs, such as acetaminophen, were involved in the incident and assess the risk for toxicity or a drug interaction.[74] Acute effects that occur after large doses of dextromethorphan are stupor, ataxia, dystonia, hyperexcitability, nystagmus, coma, and toxic psychosis. Some cases showed tachycardia, hypertension, respiratory depression, and diaphoresis.[75] In certain situations, the presence of a combination of dextromethorphan with sympathomimetic drugs (such as phenylephrine or pseudoephedrine), antihistamines (like diphenhydramine or brompheniramine), or ethanol has been associated with noticeable effects. The exact degree of toxicity resulting from the combination of pseudoephedrine and dextromethorphan is currently unknown. However, overdosing on pseudoephedrine and dextromethorphan can lead to toxic symptoms lasting for 24 hours or even longer. It is worth noting that dextromethorphan is metabolized by CYP2D6, and the presence of CYP2D6 polymorphisms can reduce its metabolism, potentially increasing toxic effects. In individuals with normal CYP2D6 function, dextromethorphan has an average elimination half-life of 2.4 hours. However, individuals with CYP2D6 polymorphisms may have an average elimination half-life of 19.1 hours. Concurrent use of dextromethorphan with substances that inhibit CYP2D6 can further prolong its elimination half-life.[76,77] Fortunately, due to the relatively short elimination time of both drugs, most toxic effects can be managed with supportive care.

Limitations

While this narrative review provides valuable insights into the safety and toxicity profile of OTC medications used for treating CCS in pediatric patients, it is essential to acknowledge several Limitations. Firstly, the review primarily relies on existing literature and may not encompass all available studies on the topic. There may be additional research studies or clinical trials that were not included in this review, potentially limiting the comprehensiveness of the findings. Secondly, the focus of this review is on clinical toxicology and the adverse effects of OTC medications, which may lead to a biased perspective on the topic. Future research should explore potential benefits, alternative treatment approaches, and the development of safer formulations to provide a more balanced understanding of the subject. Additionally, while case studies are informative, they may not always provide generalizable findings applicable to broader populations. Further research utilizing larger sample sizes and rigorous methodologies is warranted to validate the Conclusions drawn from this review. Finally, the review does not address specific regulatory aspects or policy implications related to the use of OTC medications for pediatric CCS, which could be an area for future investigation and consideration.

Conclusion

Cough and cold symptoms are commonly observed in pediatric cases, and OTC medications are frequently utilized to address these symptoms. These medications encompass a range of options, such as antihistamines (eg, CTM), decongestants (eg, pseudoephedrine), antitussives (eg, dextromethorphan), expectorants (eg, guaifenesin), and analgesics-antipyretics (eg, acetaminophen). Certain preparations combine two or more of these drugs to provide comprehensive relief. However, there are safety issues regarding the use of these medications in children, as many studies reported, as toxicity is usually an extension of their therapeutic mechanisms. Factors influencing the risk and severity of toxicity include the quantity ingested, duration of exposure, patient-specific characteristics (such as age, weight, and genetic factors), and drug-drug interactions or drug-food interactions. To minimize toxicity risks, single-agent medications are recommended over combination products, as they allow for more accurate dosing. Educating parents and caregivers about proper medication use, employing calibrated dispensing instruments, and providing clear dosing instructions are crucial steps in ensuring safety. Additionally, post-marketing surveillance is essential for monitoring potential adverse effects that may not be apparent during initial evaluations. Finally, future research should focus on the development of safer formulations and alternative treatment approaches. This could include creating medications with reduced risk profiles, exploring non-pharmacological interventions, and conducting studies to better understand the specific needs and responses of pediatric patients. By advancing our knowledge and improving the safety of treatment options, we can enhance the care and outcomes for children experiencing CCS.

Acknowledgments

The authors thank the Directorate of Research and Community Engagement of Padjadjaran University for facilitating the APC.

Disclosure

The authors declared no potential conflicts of interest to the research, authorship, or publication of this article.

References

1. Cotton M, Innes S, Jaspan H, Madide A, Rabie H. Management of upper respiratory tract infections in children. *S Afr Fam Pract*. 2008;50(2):6–12.
2. Heikkinen T, Järvinen A. The common cold. *Lancet*. 2003;361(9351):51–59. doi:10.1016/s0140-6736(03)12162-9
3. Miller SC. Dextromethorphan psychosis, dependence and physical withdrawal. *Addict Biol*. 2005;10(4):325–327. doi:10.1080/13556210500352410
4. Ryan T, Brewer M, Small L. Over-the-counter cough and cold medication use in young children. *Pediatr Nurs*. 2008;34(2):174–180.
5. Goldsobel AB, Chipps BE. Cough in the pediatric population. *J Pediatr*. 2010;156(3):352.e1–358.e1. doi:10.1016/j.jpeds.2009.12.004
6. Wazaify M, Shields E, Hughes CM, McElnay JC. Societal perspectives on over-the-counter (OTC) medicines. *Fam Pract*. 2005;22(2):170–176. doi:10.1093/fampra/cmh723
7. Slack-Smith LM, Read AW, Stanley FJ. The use of medication in children attending childcare in Western Australia. *J Paediatr Child Health*. 1998;34(2):183–187. doi:10.1046/j.1440-1754.1998.00196.x
8. Trajanovska M, Manias E, Cranswick N, Johnston L. Use of over-the-counter medicines for young children in Australia. *J Paediatr Child Health*. 2010;46(1–2):5–9. doi:10.1111/j.1440-1754.2009.01609.x
9. Isbister GK, Prior F, Kilham HA. Restricting cough and cold medicines in children. *J Paediatr Child Health*. 2012;48(2):91–98. doi:10.1111/j.1440-1754.2010.01780.x
10. Paul IM. Therapeutic options for acute cough due to upper respiratory infections in children. *Lung*. 2012;190:41–44. doi:10.1007/s00408-011-9319-y
11. Louhaichi MR, Jebali S, Loueslati MH, Adhoum N, Monser L. Simultaneous determination of pseudoephedrine, pheniramine, guaifenisin, pyrilamine, chlorpheniramine and dextromethorphan in cough and cold medicines by high-performance liquid chromatography. *Talanta*. 2009;78(3):991–997. doi:10.1016/j.talanta.2009.01.019
12. Gelotte CK, Parasrampuria DA, Zimmerman BA. Single-dose pharmacokinetics and metabolism of the oral decongestant phenylephrine HCl in children and adolescents. *Pulm Ther*. 2023;9(1):139–150. doi:10.1007/s41030-022-00206-8
13. Pappas DE, Hendley JO. The common cold and decongestant therapy. *Pediatr Rev*. 2011;32(2):47–54. doi:10.1542/pir.32-2-47
14. Carr BC. Efficacy, abuse, and toxicity of over-the-counter cough and cold medicines in the pediatric population. *Curr Opin Pediatr*. 2006;18(2):184–188. doi:10.1097/01.mop.0000193274.54742.a1
15. Smith SM, Schroeder K, Fahey T. Over-the-counter (OTC) medications for acute cough in children and adults in community settings. *Cochrane Database Syst Rev*. 2014;2014(11):CD001831. doi:10.1002/14651858.CD001831.pub5
16. Vernacchio L, Kelly JP, Kaufman DW, Mitchell AA. Pseudoephedrine use among US children, 1999–2006: results from the Slone survey. *Pediatrics*. 2008;122(6):1299–1304. doi:10.1542/peds.2008-0284
17. Horton DB, Gerhard T, Strom BL. Trends in cough and cold medicine recommendations for children in the United States, 2002–2015. *JAMA Pediatr*. 2019;173(9):885–887. doi:10.1001/jamapediatrics.2019.2252
18. Paul IM, Yoder KE, Crowell KR, et al. Effect of dextromethorphan, diphenhydramine, and placebo on nocturnal cough and sleep quality for coughing children and their parents. *Pediatrics*. 2004;114(1):e85–90. doi:10.1542/peds.114.1.e85
19. Wang GS, Green JL, Reynolds KM, et al. Trends in adverse events and related health-care facility utilization from cough and cold medication exposures in children. *Clin Toxicol*. 2021;59(4):351–354. doi:10.1080/15563650.2020.1815761
20. Kaufman DW, Kelly JP, Rosenberg L, Anderson TE, Mitchell AA. Recent patterns of medication use in the ambulatory adult population of the United States: the Slone survey. *JAMA*. 2002;287(3):337–344. doi:10.1001/jama.287.3.337
21. Dart RC, Paul IM, Bond GR, et al. Pediatric fatalities associated with over-the-counter (nonprescription) cough and cold medications. *Ann Emerg Med*. 2009;53(4):411–417. doi:10.1016/j.annemergmed.2008.09.015
22. Kelley KE, Hernández-Díaz S, Chaplin EL, Hauser R, Mitchell AA. Identification of phthalates in medications and dietary supplement formulations in the United States and Canada. *Environ Health Perspect*. 2012;120(3):379–384. doi:10.1289/ehp.1103998
23. Umar TP, Jain N, Azis H. Endemic rise in cases of acute kidney injury in children in Indonesia and Gambia: what is the likely culprit and why? *Kidney Int*. 2023;103(3):444–447. doi:10.1016/j.kint.2022.12.004
24. Payne-James J. Clinical toxicology: principles & mechanisms. *J R Soc Med*. 2004;97(11):554–555. doi:10.1177/014107680409701117
25. Routley V, Ozanne-Smith J, Ashby K. Poisonings in early childhood. *Hazard*. 1996;27:1–16.
26. Ozanne-Smith J, Routley V, Scott I, Scott G. Pharmaceutical poisoning to 0-19 year olds. *Nat Publ Health Partner Plann Pract Framew Trial*. 2002;2002:1.
27. Wang GS, Reynolds KM, Banner W, et al. Adverse events related to accidental unintentional ingestions from cough and cold medications in children. *Pediatr Emerg Care*. 2022;38(1):e100–e104. doi:10.1097/pec.0000000000002166
28. Kelley LK, Allen PJ. Managing acute cough in children: evidence-based guidelines. *Pediatr Nurs*. 2007;33(6):515–524.
29. Bell EA, Tunkel DE. Over-the-counter cough and cold medications in children: are they helpful? *Otolaryngol Head Neck Surg*. 2010;142(5):647–650. doi:10.1016/j.otohns.2010.01.019
30. Miller MR, Pronovost PJ, Burstin HR. Pediatric patient safety in the ambulatory setting. *Ambul Pediatr*. 2004;4(1):47–54. doi:10.1367/1539-4409(2004)004<0047:PPSITA>2.0.CO;2
31. Wang GS, Reynolds KM, Banner W, et al. Medication errors from over-the-counter cough and cold medications in children. *Acad Pediatr*. 2020;20(3):327–332. doi:10.1016/j.acap.2019.09.006

32. At Thobari J, Satria CD, Ridora Y, et al. Non-antibiotic medication use in an Indonesian community cohort 0-18 months of age. *PLoS One*. 2020;15(11):e0242410. doi:10.1371/journal.pone.0242410
33. Yust E, Slattery A. Cold and cough medications for children: dangerous and over the counter! *Clin Pediatr Emerg Med*. 2012;13(4):292–299. doi:10.1016/j.cpem.2012.09.007
34. Gitawati R. Active ingredients in cough and cold combinations and how to choose a rationale drug. *Med Penelit Dan Pengemb Keseh*. 2014;24:10–18. doi:10.22435/mpk.v24i1.3482.10-18
35. Kelly LF. Pediatric cough and cold preparations. *Pediatr Rev*. 2004;25(4):115–123. doi:10.1542/pir.25-4-115
36. Soedibyo S, Yulianto A, Wardhana W. The profile of OTC cough and cold drugs for pediatric patients under 6 years old. *Sari Pediatri*. 2016;14(6):398. doi:10.14238/sp14.6.2013.398-404
37. Raiborde MD, Kumar G, Singh P, Sharma S. Dextromethorphan an emerging drug of abuse. *J Pharm Negat Res*. 2022;609–621. doi:10.47750/pnr.2022.13.S06.087
38. Dicpinigaitis PV, Gayle YE, Solomon G, Gilbert RD. Inhibition of cough-reflex sensitivity by benzonatate and guaifenesin in acute viral cough. *Respir Med*. 2009;103(6):902–906. doi:10.1016/j.rmed.2008.12.008
39. Przybyła GW, Szychowski KA, Gmiński J. Paracetamol - An old drug with new mechanisms of action. *Clin Exp Pharmacol Physiol*. 2021;48(1):3–19. doi:10.1111/1440-1681.13392
40. Halmo LS, Wang GS, Reynolds KM, et al. Pediatric fatalities associated with over-the-counter cough and cold medications. *Pediatrics*. 2021;148(5):e2020049536. doi:10.1542/peds.2020-049536
41. Vassilev ZP, Kabadi S, Villa R. Safety and efficacy of over-the-counter cough and cold medicines for use in children. *Expert Opin Drug Saf*. 2010;9(2):233–242. doi:10.1517/14740330903496410
42. Sen EF, Verhamme KMC, Felisi M, et al. Effects of safety warnings on prescription rates of cough and cold medicines in children below 2 years of age. *Br J Clin Pharmacol*. 2011;71(6):943–950. doi:10.1111/J.1365-2125.2010.03860.X
43. Shastry BS. Pharmacogenomics and its importance in pediatric medicine. *J Pediatr Genet*. 2012;1(2):79–84. doi:10.3233/pge-2012-015
44. Shastry BS. Pharmacogenomics and Pharmacoepigenomics in Pediatric Medicine. In: Yan Q, editor. *Pharmacogenomics in Drug Discovery and Development. Methods in Molecular Biology*. Vol. 1175. New York, NY: Humana Press; 2014. doi:10.1007/978-1-4939-0956-8_18
45. Wang H, Shi H, Wang N, et al. Prevalence of potential drug-drug interactions in the cardiothoracic intensive care unit patients in a Chinese tertiary care teaching hospital. *BMC Pharmacol Toxicol*. 2022;23(1):39. doi:10.1186/s40360-022-00582-6
46. Anderson WIB, Benowitz NL, Blanc PD, et al. *Poisoning and Drug Overdose*. 7th ed. Olson KR, ed. McGraw Hill Medical; 2018.
47. Fitzsimons R, van der Poel LA, Thornhill W, et al. Antihistamine use in children. *Arch Dis Child Educ Pract Ed*. 2015;100(3):122–131. doi:10.1136/archdischild-2013-304446
48. Helal RM, Abou-ElWafa HS. Self-medication in university students from the City of Mansoura, Egypt. *J Environ Public Health*. 2017;2017:1–7. doi:10.1155/2017/9145193
49. Paul IM, Reynolds KM, Kauffman RE, et al. Adverse events associated with pediatric exposures to dextromethorphan. *Clin Toxicol*. 2017;55(1):25–32. doi:10.1080/15563650.2016.1240803
50. Patil SB, Vardhamane SH, Patil BV, Santoshkumar J, Binjawadgi AS, Kanaki AR. Self-medication practice and perceptions among undergraduate medical students: a cross-sectional study. *J Clin Diagn Res*. 2014;8(12):HC20. doi:10.7860/JCDR/2014/10579.5313
51. Silva AR, Dinis-Oliveira RJ. Pharmacokinetics and pharmacodynamics of dextromethorphan: clinical and forensic aspects. *Drug Metab Rev*. 2020;52:258–282. doi:10.1080/03602532.2020.1758712
52. Klotz U. Paracetamol (Acetaminophen) - A popular and widely used nonopioid analgesic. *Arzneimittelforschung*. 2012;62:355–359. doi:10.1055/s-0032-1321785
53. Kleiber N, Calvier E, Mooij MG, et al. Enteral Acetaminophen bioavailability in pediatric intensive care patients determined with an oral microtracer and pharmacokinetic modeling to optimize dosing. *Crit Care Med*. 2019;47:e975–e983. doi:10.1097/ccm.0000000000004032
54. Zuppa AF, Hammer GB, Barrett JS, et al. Safety and population pharmacokinetic analysis of intravenous Acetaminophen in neonates, infants, children, and adolescents with pain or fever. *J Pediatr Pharmacol Ther*. 2011;16:246. doi:10.5863/1551-6776-16.4.246
55. Simons FER, Gu X, Watson WTA, Simons KJ. Pharmacokinetics of the orally administered decongestants pseudoephedrine and phenylpropanolamine in children. *J Pediatr*. 1996;129:729–734. doi:10.1016/S0022-3476(96)70157-9
56. Swanson-Biearman B. Pseudoephedrine. *Encyclop Toxicol*. 2005;556–557. doi:10.1016/B0-12-369400-0/00811-5
57. Głowacka K, Wiela-Hojeńska A. Pseudoephedrine-benefits and risks. *Int J Mol Sci*. 2021;22(10):5146. doi:10.3390/ijms22105146
58. Guenin E, Armogida M, Riff D. Pharmacokinetic profile of dextromethorphan hydrobromide in a syrup formulation in children and adolescents. *Clin Drug Investig*. 2014;34:609–616. doi:10.1007/S40261-014-0210-5/METRICS
59. Kukanich B, Papich MG. Plasma profile and pharmacokinetics of dextromethorphan after intravenous and oral administration in healthy dogs. *J Vet Pharmacol Ther*. 2004;27(5):337–341. doi:10.1111/j.1365-2885.2004.00608.x
60. Liang MD, Ivan E, Boyer EW. Dissociative agents: phencyclidine, ketamine and dextromethorphan. In: *Haddad and Winchester's Clinical Management of Poisoning and Drug Overdose*. 4th ed. ScienceDirect; 2007.
61. Simons FER, Luciuk GH, Simons KJ. Pharmacokinetics and efficacy of chlorpheniramine in children. *J Allergy Clin Immunol*. 1982;69:376–381. doi:10.1016/0091-6749(82)90149-X
62. Martínez-Gómez MA, Villanueva-Camañas RM, Sagrado S, Medina-Hernández MJ. Evaluation of enantioselective binding of antihistamines to human serum albumin by ACE. *Electrophoresis*. 2007;28(15):2635–2643. doi:10.1002/elps.200600742
63. Sharma A, Hamelin B. Classic histamine H1 receptor antagonists: a critical review of their metabolic and pharmacokinetic fate from a bird's eye view. *Curr Drug Metab*. 2005;4:105–129. doi:10.2174/1389200033489523
64. Hua YM, Hung CH, Yuh YS. Acute intoxication of lidocaine and chlorpheniramine: report of one case. *Acta Paediatr Taiwan*. 2005;46(6):385–387.
65. Lista AD, Sirimaturos M. Pharmacokinetic and pharmacodynamic principles for toxicology. *Crit Care Clin*. 2021;37(3):475–486. doi:10.1016/j.ccc.2021.03.001
66. Park YC, Lee S, Cho MH. The simplest flowchart stating the mechanisms for organic xenobiotics-induced toxicity: can it possibly be accepted as a "central dogma" for toxic mechanisms? *Toxicol Res*. 2014;30:179–184. doi:10.5487/tr.2014.30.3.179
67. Athersuch TJ, Antoine DJ, Boobis AR, et al. Paracetamol metabolism, hepatotoxicity, biomarkers and therapeutic interventions: a perspective. *Toxicol Res*. 2018;7(3):347–357. doi:10.1039/c7tx00340d

68. Lowry JA, Leeder JS. Over-the-counter medications: update on cough and cold preparations. *Pediatr Rev*. 2015;36(7):286–297. doi:10.1542/pir.36-7-286
69. Palmer RB, Reynolds KM, Banner W, et al. Adverse events associated with diphenhydramine in children, 2008–2015. *Clin Toxicol*. 2020;58(2):99–106. doi:10.1080/15563650.2019.1609683
70. Soyer T, Göl IH, Eroğlu F, Cetin A. Acute urinary retention due to pseudoephedrine hydrochloride in a 3-year-old child. *Turk J Pediatr*. 2008;50(1):98–100.
71. Roberge RJ, Hirani KH, Rowland PL, Berkeley R, Krenzelok EP. Dextromethorphan- and pseudoephedrine-induced agitated psychosis and ataxia: case report. *J Emerg Med*. 1999;17:285–288. doi:10.1016/s0736-4679(98)00193-0
72. Glidden RS, DiBona FJ. Urinary retention associated with ephedrine. *J Pediatr*. 1977;90:1013–1014. doi:10.1016/s0022-3476(77)80584-2
73. Rüdesheim S, Selzer D, Fuhr U, Schwab M, Lehr T. Physiologically-based pharmacokinetic modeling of dextromethorphan to investigate interindividual variability within CYP2D6 activity score groups. *CPT*. 2022;11(4):395–524. doi:10.1002/psp4.12776
74. Gatti JM, Perez-Brayfield M, Kirsch AJ, Smith EA, Massad HC, Broecker BH. Acute urinary retention in children. *J Urol*. 2001;165:918–921. doi:10.1016/S0022-5347(05)66574-3
75. Chyka PA, Erdman AR, Manoguerra AS, et al. American association of poison control centers. Dextromethorphan poisoning: an evidence-based consensus guideline for out-of-hospital management. *Clin Toxicol*. 2007;45(6):662–677. doi:10.1080/15563650701606443
76. Seltzer JA, Sheth SK, Friedland S, et al. Life-threatening pediatric dextromethorphan polistirex overdose. *AmJ Emerg Med*. 2022;61:233.e1–233.e2. doi:10.1016/j.ajem.2022.08.006
77. Capon DA, Bochner F, Kerry N, Mikus G, Danz C, Somogyi AA. The influence of CYP2D6 polymorphism and quinidine on the disposition and antitussive effect of dextromethorphan in humans. *Clin Pharmacol Ther*. 1996;60:295–307. doi:10.1016/s0009-9236(96)90056-9