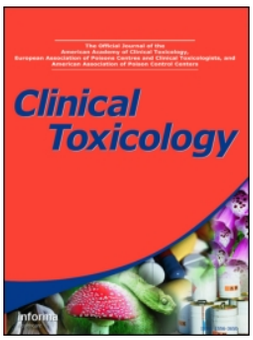

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CLINICAL RESEARCH

Adverse events associated with pediatric exposures to dextromethorphan

Ian M. Paul[a], Kate M. Reynolds[b], Ralph E. Kauffman[c], William Banner[d], G. Randall Bond[e], Robert B. Palmer[b], Randy I. Burnham[b] and Jody L. Green[b]

[a]Pediatrics & Public Health Sciences, Penn State College of Medicine, Hershey, PA, USA; [b]Rocky Mountain Poison and Drug Center, Denver Health and Hospital Authority, Denver, CO, USA; [c]Department of Pediatrics, University of Missouri-Kansas City School of Medicine, Kansas City, MO, USA; [d]Oklahoma Center for Poison and Drug Information, Oklahoma University College of Pharmacy, Oklahoma City, OK, USA; [e]School of Medicine, Hope Africa University, Bujumbura, Burundi

ABSTRACT

Study objective: Dextromethorphan is the most common over-the-counter (OTC) antitussive medication. We sought to characterize adverse events associated with dextromethorphan in children <12 years old from a surveillance program of OTC cough/cold medication exposures.

Methods: This is a retrospective case series of oral exposures to dextromethorphan with ≥1 adverse event from multiple U.S. sources (National Poison Data System, FDA Adverse Event Reporting System, manufacturer safety reports, news/media, medical literature) reported between 2008 and 2014. An expert panel determined the relationship between exposure and adverse events, estimated dose ingested, intent of exposure, and identified contributing factors to exposure.

Results: 1716 cases contained ≥1 adverse event deemed at least potentially related to dextromethorphan; 1417 were single product exposures. 773/1417 (55%) involved only one single-ingredient dextromethorphan product (dextromethorphan-only). Among dextromethorphan-only cases, 3% followed ingestion of a therapeutic dose; 78% followed an overdose. 69% involved unsupervised self-administration and 60% occurred in children <4 years old. No deaths or pathologic dysrhythmias occurred. Central nervous system [e.g., ataxia ($N = 420$)] and autonomic symptoms [e.g., tachycardia ($N = 224$)] were the most common adverse events. Flushing and/or urticarial rash occurred in 18.1% of patients. Dystonia occurred in 5.4%.

Conclusions: No fatalities were identified in this multifaceted surveillance program following a dextromethorphan-only ingestion. Adverse events were predominantly associated with overdose, most commonly affecting the central nervous and autonomic systems.

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Dextromethorphan; cough; adverse events; poison control centers

Introduction

Background

Over-the-counter (OTC) drugs are common medications involved in pediatric overdoses, emergency department (ED) visits, and poison center calls.[1–3] Cough/cold medications as a class have been targeted as a cause of pediatric morbidity, particularly when ingested by young children,[4–6] but limited data exist examining individual drugs, and how children might clinically present following therapeutic exposures versus an overdose.

Three non-prescription oral, OTC drug ingredients are labeled for use as antitussives in children by the U.S. Food and Drug Administration (FDA) in the Cough, Cold, Allergy, Bronchodilator and Asthmatic Drug Products for Over-the-Counter Human Use Final Monograph (21 CFR 341): dextromethorphan, chlophedianol, and diphenhydramine.[7] Dextromethorphan is the most common drug administered to children solely for antitussive purposes, and chlophedianol is not widely available in the U.S.A.[8,9] While diphenhydramine also is approved for use as an antitussive in children, its initial and primary indication is as an antihistamine for allergic conditions.[10]

Importance

In 2007 and 2008, voluntary changes to the labels of cough/cold medications used in children were made by OTC manufacturers with FDA support. These changes included modifications to the label to "do not use" in children <4 years of age, which followed voluntary removal of all infant concentrations of cough/cold medications. Despite these voluntary changes, several recent studies indicate that cough/cold medications, such as dextromethorphan, continue to have wide acceptance by parents for use in children.[11–14] However, the American Academy of Pediatrics does not support the use of dextromethorphan in children citing questionable efficacy and safety concerns.[15,16] The safety concerns for children are based primarily on anecdotal case reports, small series of cases, small clinical trials, and data extrapolated from adults. As such, the association between dextromethorphan use in children and the reported safety concerns has not been rigorously evaluated.

In addition to concerns related to pediatric exposures involving use of dextromethorphan as directed by the product label, real-world conditions also lead to exposures in children that are more variable. Unintended self-administration

CONTACT Jody L. Green Jody.green@rmpdc.org Rocky Mountain Poison and Drug Center, Denver Health and Hospital Authority, 777 Bannock Street, MC 0180, Denver, CO 80204, USA

occurs when exploring children ingest these products, often leading to amounts that exceed recommended therapeutic doses. In addition, dextromethorphan is available in a wide variety of products including adult cough/cold preparations, which are frequently available in the homes where children are present, contributing to both unsupervised ingestions, drug abuse and self-harm exposures in older children. Children may also receive excessive doses when caregivers administer the more concentrated adult preparations to the child or when the child self-administers them. Other factors may also lead to an excessive dose, including failure to use appropriate measuring devices, dosing too frequently, or concurrent dosing with two different products both containing dextromethorphan.

Goals of this investigation

In light of the availability of OTC dextromethorphan products and continuing concern about their safety, particularly for younger children, we sought to characterize the adverse events associated with dextromethorphan exposures in children <12 years old. While adverse events occur following consumption of both single ingredient and combination products containing dextromethorphan, this analysis of the morbidities associated with dextromethorphan-related events is limited to exposures to single ingredient dextromethorphan preparations to avoid confounding from co-administration of other drugs. This analysis will therefore inform ED providers and poison centers on the common constellation of symptoms and scenarios that follow pediatric ingestions of dextromethorphan.

Patients and methods

Study design and setting

This study was done as part of a multi-year safety surveillance program directed by the Rocky Mountain Poison and Drug Center to assess safety of OTC medications used in cough/cold products in children <12 years old. This program was designed to (1) conduct ongoing safety surveillance by monitoring for adverse events associated with exposure to oral OTC cough/cold medications in children <12 years old and (2) perform root cause analysis to characterize risk factors for toxic effects associated with oral cough/cold medication exposures in children <12 years of age. Cases meeting inclusion criteria are collected from multiple sources: National Poison Data System of the American Association of Poison Control Centers, FDA Adverse Event Reporting System, news and media reports, English language medical literature, and participating manufacturer safety reports. Case inclusion criteria are child <12 years old, oral exposure to one or more of eight index cough/cold ingredients (brompheniramine, chlorpheniramine, dextromethorphan, diphenhydramine, doxylamine, guaifenesin, phenylephrine, pseudoephedrine), report of a significant clinical effect, and the exposure having occurred in the U.S.A. Duplicate cases from multiple sources were identified using the Guideline on Detection and Management of Duplicate Individual Cases and Individual Case Safety Reports standards and were combined into a single case record.[17]

Selection of participants

For this analysis, a sub-group of cases involving exposure to products that include dextromethorphan as an ingredient were selected from the larger surveillance study of pediatric cough/cold medication exposures. Case inclusion criteria for analysis of this sub-group of cases were oral exposure to dextromethorphan, report of a clinical adverse event associated with the dextromethorphan exposure, report detected between 1 January 2008 and 31 March 2015, with an adverse event that occurred between 1 January 2008 and 31 December 2014.

Outcome measures

A panel organized by RMPDC was formed consisting of experts in the fields of pediatrics (I.M.P., R.E.K., G.R.B., W.B.), pediatric critical care medicine (W.B.), pediatric emergency medicine (G.R.B.), pediatric pharmacology (R.E.K.), pediatric toxicology (G.R.B., W.B.), and clinical and forensic toxicology (R.B.P.). Selection of panel members was based on evidence of previous research and clinical experience involving the toxicity of cough/cold medication ingredients in children. Each panelist reviewed all case abstracts, as well as all source materials on each case individually.

Eligible cases were evaluated by the expert panel to determine a causal relationship between exposure and event, categorize the likely dose ingested, and identify contributing factors of the exposure. The relationship between each adverse event and dextromethorphan exposure was assigned to one of four categories: related, potentially related, unlikely related, and unable to determine (Table 1). The expert panel assigned the intent of dextromethorphan administration to one of three categories: therapeutic, non-therapeutic (including child self-administration), or unknown. Panel members independently reviewed each case and all final decisions by the panel were formed during face-to-face meetings or conference calls. Decisions were based on the entire body of

Table 1. Factors used to determine adverse event relationship to drug exposure.

Related
• History of ingestion consistent with exposure
• Drug levels consistent with exposure, if available
• Clinical course consistent with exposure
• No other cause of death/event evident
Potentially related
• History of ingestion consistent with exposure
• Drug levels consistent with exposure, if available
• Clinical course consistent with exposure
• Other cause of death/event unlikely
• Drug may have been secondary cause of death/event
Unlikely Related
• No history of ingestion
• Drug levels inconsistent with exposure
• Clinical course inconsistent with exposure
• Other cause of death/event possible
Unable to determine
• Not enough case detail to evaluate relationship of drug to death/event

information available for each case using a priori rules. Cases for which there was initial disagreement among the panel members were re-reviewed and debated by the panel until 100% consensus was reached on every case.

Ingestions were categorized as to the number of specific products involved, by the number of ingredients present in each product, and by the product type. Products were classified by dosage formulation (liquid, solid, unknown) and age formulation (pediatric, adult, unknown). Age formulation was determined by the product labeling for a given product, with products providing dosing instructions for children under the age of 12 years categorized as pediatric formulation and products containing only dosing for adolescents and adults over the age of 12 years categorized as adult formulation.

Although precise doses often could not be determined from available information in the case narrative, exposures were assigned to one of three dose categories, therapeutic, supratherapeutic, or unknown, based on established monograph dosing guidelines for dextromethorphan hydrobromide [7] and, where available, child-specific research.[18] For extended release preparations containing dextromethorphan polistirex, doses in approved monograph labeling were used as the reference standard. In cases involving ingestion of dextromethorphan polistirex by children who were younger than the approved age range in the monograph label, the panel extrapolated the dose of the twice daily preparation to its shorter acting four times daily version.

Adverse events were defined as any untoward medical occurrence including unfavorable and unintended signs (e.g., abnormal laboratory findings), symptoms, or diseases temporally associated with the use of the product as reported by the parent, caregiver, or medical personnel.[17] Each adverse event reported in the case narrative or as a coded clinical effect among cases from the National Poison Data System, FDA Adverse Event Reporting System, and manufacturer safety databases were extracted and evaluated for causality. Each adverse event term was coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 17.0 (MSSO, McLean, VA). Each verbatim adverse event term was coded to the closest MedDRA lower level term by a trained MedDRA coder using a standardized process applied to terms from all data sources. MedDRA preferred terms occurring in at least 5% of cases are reported for this analysis.

Analysis

Cases with at least one adverse event determined to be at least potentially related (potentially related or related) to dextromethorphan were included. Case characteristics, panel assessments, and adverse events are presented using descriptive statistics. Categorical outcomes are summarized by their frequency and results are stratified by type of product, age group, and dose. The number of unique preferred term adverse events per subject were compared across dose groups using the Kruskal–Wallis one-way analysis of variance. Adverse event results are presented only for single ingredient–single product dextromethorphan exposures (i.e., an exposure only to dextromethorphan) to avoid confounding by exposure to concomitant drugs. Analyses were performed using SAS software, version 9.3 (SAS Institute Inc., Cary, NC). $p < 0.05$ was considered statistically significant.

Results

Cases and product formulations

Among 5342 individual cases involving OTC cough/cold products reviewed by the expert panel during the 7-year period, 1716 (32.1%) reported at least one adverse event deemed at least potentially related to dextromethorphan. These 1716 cases came from the National Poison Data System ($n = 1599$), FDA Adverse Event Reporting System ($n = 35$), news and media reports ($n = 1$), participating manufacturer safety reports ($n = 91$). No cases were received from the medical literature and 18 records were duplicates from multiple sources condensed into 8 unique records. Single-product, single-ingredient dextromethorphan exposures (dextromethorphan-only) accounted for 773 or nearly half (45.0%) of the total dextromethorphan exposures. The remaining dextromethorphan cases involved a single combination cough/cold product ($n = 644$; 37.5%), a dextromethorphan-containing product plus another product ($n = 296$; 17.2%), or an unknown number of products ($n = 3$, 0.2%) (Figure 1).

Liquid preparations were involved in 99.2% of dextromethorphan-only cases with pediatric liquid products accounting for 95.0% of exposures. Notably, among dextromethorphan-only cases, the liquid extended-release formulation of dextromethorphan, dextromethorphan polistirex, was responsible for virtually all 724/773 (93.7%) cases.

Adverse events

No deaths or pathologic cardiac dysrhythmias were reported among dextromethorphan-only cases. The adverse event profile was dominated by central nervous system and autonomic symptoms following dextromethorphan-only ingestions, with ataxia, somnolence, mydriasis, tachycardia, and hallucinations each occurring in >20% of cases regardless of whether the dose was supratherapeutic, therapeutic, or unknown (Table 2). A generalized flushing or rash often with urticaria was reported in 140 cases (18.1%). Dystonia occurred in 5.4%. Notably less common, occurring in 3.5% of cases ($n = 27$), were respiratory adverse events, including MedDRA preferred adverse event terms of hypoxia, respiratory depression, apnea, decreased respiratory rate, hypopnea, hypoventilation, respiratory disorder, and respiratory failure.

Only 22 (2.8%) of dextromethorphan-only cases involved a therapeutic dose, while the majority involved supratherapeutic doses ($n = 603$; 78.0%) (dose could not be determined in 148; 19.1%). Although limited by the small number of therapeutic dose cases, the difference in the median number of unique adverse events between children ingesting a supratherapeutic dose and those ingesting a therapeutic dose was borderline significant ($p = 0.054$), where the number of reported adverse events in supratherapeutic dose cases ranged from 1 to 15 (median: 4) versus 1 to 10 (median: 3) for therapeutic dose cases. Some children with a substantial

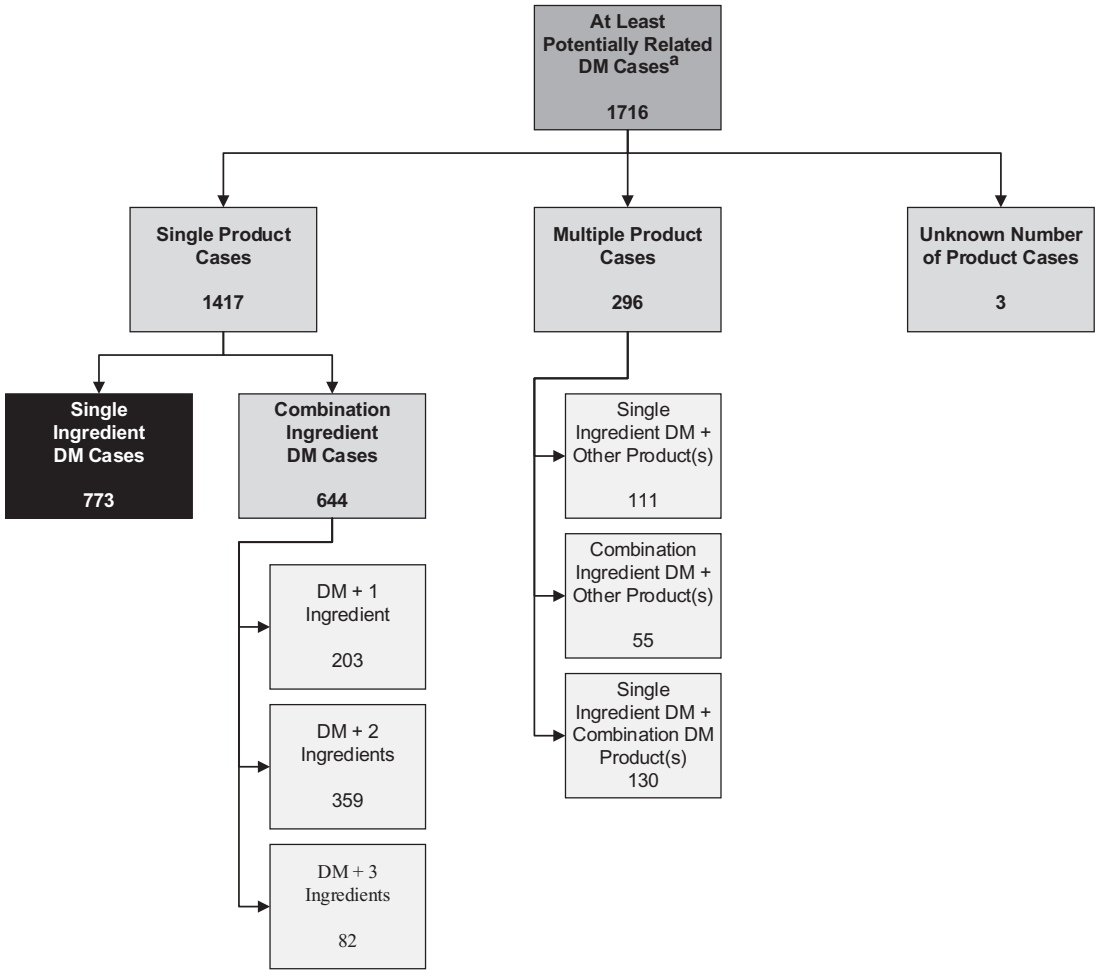

Figure 1. Cases with at least one adverse event related to dextromethorphan 2008–2014.
[a]Cases were collected from the National Poison Data System of the American Association of Poison Control Centers, FDA Adverse Event Reporting System, news and media reports, English language medical literature, and participating manufacturer safety reports.

Table 2. Adverse events[a] associated with single ingredient dextromethorphan ingestion by evaluated dose range.

MedDRA preferred term	Total $N = 773$	Therapeutic dose $N = 22$	Supratherapeutic dose $N = 603$	Unknown dose $N = 148$
Ataxia	420 (54.3%)	4 (18.2%)	328 (54.4%)	88 (59.5%)
Somnolence	307 (39.7%)	2 (9.1%)	260 (43.1%)	45 (30.4%)
Mydriasis	234 (30.3%)	6 (27.3%)	190 (31.5%)	38 (25.7%)
Tachycardia	224 (29.0%)	3 (13.6%)	180 (29.9%)	41 (27.7%)
Hallucination	187 (24.2%)	7 (31.8%)	149 (24.7%)	31 (20.9%)
Nystagmus	155 (20.1%)	1 (4.5%)	125 (20.7%)	29 (19.6%)
Confusional state	149 (19.3%)	1 (4.5%)	119 (19.7%)	29 (19.6%)
Dizziness	93 (12.0%)	2 (9.1%)	77 (12.8%)	14 (9.5%)
Dysarthria	92 (11.9%)	1 (4.5%)	70 (11.6%)	21 (14.2%)
Flushing	91 (11.8%)	0 (0.0%)	75 (12.4%)	16 (10.8%)
Vomiting	91 (11.8%)	0 (0.0%)	74 (12.3%)	17 (11.5%)
Irritability	90 (11.6%)	2 (9.1%)	74 (12.3%)	14 (9.5%)
Hypertension	89 (11.5%)	3 (13.6%)	68 (11.3%)	18 (12.2%)
Lethargy	78 (10.1%)	0 (0.0%)	58 (9.6%)	20 (13.5%)
Psychomotor hyperactivity	72 (9.3%)	3 (13.6%)	63 (10.4%)	6 (4.1%)
Abnormal behavior	68 (8.8%)	1 (4.5%)	48 (8.0%)	19 (12.8%)
Pyrexia	60 (7.8%)	1 (4.5%)	47 (7.8%)	12 (8.1%)
Agitation	57 (7.4%)	4 (18.2%)	41 (6.8%)	12 (8.1%)
Staring	44 (5.7%)	1 (4.5%)	30 (5.0%)	13 (8.8%)
Dystonia	42 (5.4%)	1 (4.5%)	32 (5.3%)	9 (6.1%)

[a]Adverse event terms occurring in at least 5% of cases are presented.

overdose experienced relatively minimal symptoms, whereas others with lesser overdose reported multiple severe adverse events. Notably, ataxia (OR: 5.4, 95% CI: 1.8, 16.1) and somnolence (OR: 7.6, 95% CI: 1.8, 32.7) were more likely to occur with a supratherapeutic dose than with therapeutic dose, and no commonly reported adverse events (adverse events reported in 2% or more of cases) were more likely to occur in therapeutic dose cases.

Table 3. Case characteristics of dextromethorphan exposures.

Case characteristics	Total $N = 773$
Age group	
Less than 2 years	57 (7.4%)
2 to <4 years	404 (52.3%)
4 to <6 years	196 (25.4%)
6 to <12 years	116 (15.0%)
Sex	
Female	349 (45.1%)
Male	424 (54.9%)
Panel evaluated dose	
Supratherapeutic dose	603 (78.0%)
Therapeutic dose	22 (2.8%)
Unknown dose	148 (19.1%)
Product form	
Liquid, pediatric	734 (95.0%)
Liquid, unknown	23 (3.0%)
Liquid, adult	9 (1.2%)
Solid, adult	4 (0.5%)
Solid, pediatric	2 (0.3%)
Unknown, unknown	1 (0.1%)

Demographic associations

Children <4 years old comprised the largest group of dextromethorphan-only cases ($n = 461$; 59.6%), whereas children aged 6 to <12 years were least frequently represented ($n = 116$; 15.0%) (Table 3). Males were over-represented (54.9% of cases). The majority of dextromethorphan-only cases overall involved accidental unsupervised ingestions (69.3%), and this was particularly common among children aged <4 years (85.9%; 396/461). Therapeutic intent was the dominant intent in cases where adverse events occurred among children aged 6 to <12 years (54.3%).

Limitations

This study is limited by the few cases of adverse events following therapeutic dose ingestions, making it difficult to precisely characterize the frequency of adverse events among those without an overdose. Alternatively, it suggests the probability that recommended therapeutic doses rarely result in reportable adverse events. The focus on dextromethorphan-only cases in this study does not allow for evaluation of drug–drug interactions, which would be the subject of a separate analysis and report. In many cases, a good history of context of exposure was not available – whether it was the patient's medicine, medicine of siblings, parent's medicine, and whether the medicine was stored and found by the child or had been left out for use. Given the nature of data sources for this study, primary medical records rarely were available. This limited the ability to verify the actual existence of certain findings and presented the possibility that pertinent information existed but were unavailable for case review. Further, this study is somewhat limited by the variable quality of and detail in the case narratives used for analysis. As such, the most dramatic findings are most likely to be noted and mentioned in the sources available (e.g., hallucinations, ataxia, nystagmus, flushing), but the frequency of all these adverse event observations should be considered a minimum due to the potential for underreporting of these data sources.

Discussion

The 1716 total cases reported here including 773 dextromethorphan-only ingestions were collected from across the U.S.A. over a 7-year period, representing the most comprehensive characterization of adverse events associated with dextromethorphan in children. The absence of deaths and pathologic cardiac events in children with single-ingredient dextromethorphan exposure provide some reassurance of safety, though deaths within the home may not have been captured by this surveillance system. The morbidities associated with dextromethorphan observed in young children in this study are consistent with the known pharmacologic actions of dextromethorphan and its active metabolites,[19] and the list of observed effects can also serve ED and poison center providers confronted with a patient with an unclear drug-exposure history.

Two groups of symptoms dominated in our cohort: central nervous system and autonomic. Ataxia, hallucinations, agitation, and nystagmus are among the most distressing to parents and temporarily debilitating to children. Tachycardia, hypertension, mydriasis, and temperature elevation tended to resolve spontaneously without significant consequences. Our study supports an adverse event profile similar to that previously published in case reports and smaller case series,[20–27] but the presence of central nervous system effects in some, but certainly not all, children with supratherapeutic exposures suggests that some children may be more susceptible to these effects of dextromethorphan. This finding is similar to that seen in adolescent and adults abusing dextromethorphan.[28,29]

Adverse events associated with dextromethorphan are thought to be related to both the parent drug and its active metabolites, particularly dextrorphan. Although dextromethorphan is structurally related to levorphanol, a μ-opioid agonist, it has little or no affinity for the μ receptor group, which likely accounts for the low incidence of respiratory effects observed in the dextromethorphan-only cases. The main site of action of dextromethorphan is thought to be as a non-competitive central antagonist at the NMDA receptor complex.[30,31] It also may have pro-serotonergic activity.[32] The antitussive action of dextromethorphan has been attributed to inhibition of NMDA receptors in the medullary cough center.[33,34] Dextromethorphan is metabolized primarily by cytochrome P450 2D6-mediated (CYP2D6) O-demethylation to the dominant active metabolite, dextrorphan.[35] Dextrorphan also is an NMDA inhibitor and has no opioid agonist activity.[36,37] Two additional metabolites, 3-methoxymorphinan and 3-hydroxymorphinan, are formed by a relatively minor N-demethylation pathway mediated by cytochrome 3A [35,38] (Figure 2).

CYP2D6, the enzyme mediating the primary metabolic pathway for dextromethorphan, is highly polymorphic in the North American population with 5–10% of individuals carrying allelic variants resulting in decreased activity of the

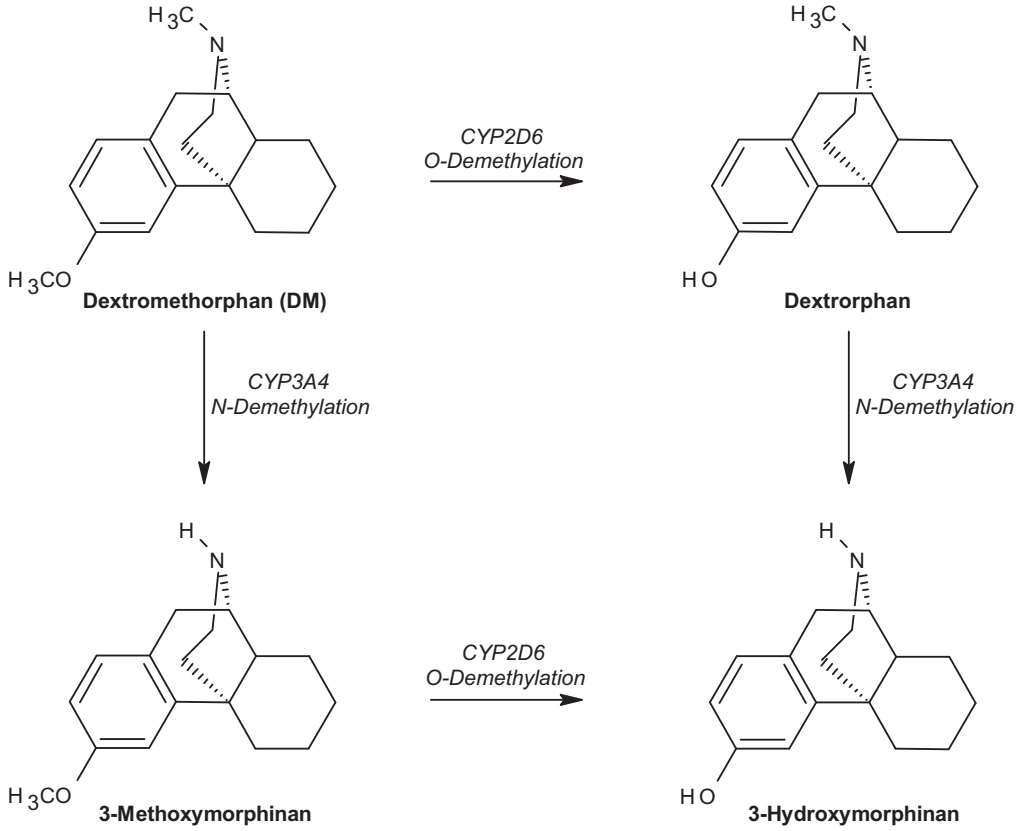

Figure 2. Metabolism of dextromethorphan.

enzyme that make them poor metabolizers of dextromethorphan.[39,40] CYP2D6 activity is well expressed postnatally, so that genotype and phenotype are concordant by 2 weeks of age.[35] Mean half-life of dextromethorphan in children who are not poor metabolizers is 4–7 h.[41] Because of the relatively short half-life, particularly in younger children, a liquid polistirex formulation is available as a sustained-release preparation to provide a longer duration of action following a dose.

CYP2D6 polymorphism may have a profound effect on the susceptibility of an individual to adverse events following a given dose of dextromethorphan, including recommended therapeutic doses. Studies in adult subjects have shown that the psychotropic effects of dextromethorphan, including sedation, dysphoria, and psychomotor impairment, are increased in the presence of decreased CYP2D6 activity.[36,42] Type and severity of adverse events are also dose dependent. Adult subjects receiving high doses of dextromethorphan (100 mg/70 kg up to 800 mg/70 kg) in a controlled dose ranging study experienced significant CNS and autonomic symptoms including increased blood pressure, increased heart rate, emesis, visual effects, perceptual changes, and dissociative effects similar to classic hallucinogens.[37] This is consistent with the adverse events we observed in children, particularly in the supratherapeutic exposure group. A wide range of type and severity of adverse events occurred in children whose dextromethorphan exposure was judged to be supratherapeutic. This was partly due to lack of precision in estimating the exposure dose based on available information. However, genetic variation in CYP2D6 activity undoubtedly also contributed to variation in incidence and severity of adverse events. Unfortunately, we had no genetic information on any of the cases with which to assess this.

The frequency of flushing and allergic-like skin reactions (18.1%) is noteworthy, though true anaphylaxis was not described. The flushing was often treated by diphenhydramine but the effectiveness of that therapy was not clear. The mechanism of the cutaneous reaction was also not clear.

In a study of the impact of labeling changes on the number of ED visits for cough/cold medication toxicity, Hampton et al. estimated that in the period overlapping our study, about 68% of cases involved children under age 4 with 80% of these exposures following child self-ingestion. In contrast, in children 6–11 years of age, 82% involved therapeutic use with incorrect dosing. Although their estimates involved all cough/cold medications presenting to an ED and ours are limited to symptomatic dextromethorphan exposures, the results are similar.[43]

The predominance of dextromethorphan-only liquid preparations in our study may be a feature of product availability or accessibility/preference by children. Certainly one would expect medications intentionally given to children to be predominantly liquid – whether they were pediatric or adult products. Because the majority of cases in this study were due to accidental unsupervised ingestions, reducing access to medications in the home and improving child-resistant packaging promise to be the most effective interventions to reduce dextromethorphan adverse events.

We specifically excluded multi-ingredient OTC dextromethorphan products, multiple-product exposures, and all non-

OTC dextromethorphan containing products from our adverse event analysis. Multi-ingredient OTC cough/cold products often contain a combination of dextromethorphan with diphenhydramine, brompheniramine, or chlorpheniramine; pseudoephedrine, ephedrine, or phenylephrine; guaifenesin, and/or acetaminophen. The potential effects of these medications on the central nervous system, including pupil size, heart rate, blood pressure, and temperature led us to exclude these cases from the analysis since we were primarily interested in evaluating dextromethorphan effects for this report. We also excluded ingestions of more than one product since the second product often was a prescription product, sometimes including clonidine or an opioid. Furthermore, a disproportionate number of multiple product cases involved children more than 6 years of age, including suicidal children and children indulging in substance abuse. Finally, many of the prescription cough/cold products contained codeine or promethazine as the other ingredient, thereby obscuring the effects of dextromethorphan.

We report the most comprehensive data to date on adverse events associated with OTC cough/cold products containing dextromethorphan as the sole active ingredient. These events occur most commonly among boys <4 years old following the accidental unsupervised ingestion of supratherapeutic doses of liquid medication preparations. The symptom pattern is primarily related to central and autonomic nervous system effects, and ED and poison center providers should consider dextromethorphan as an exposure for those presenting with this constellation of symptoms. Death and pathologic cardiac dysrhythmias were not observed in pure dextromethorphan ingestions, even in the highest doses. Efforts to reduce such ingestions should focus on reducing a child's access to these medications by continuing to encourage safe medication storage and improving child-resistant packaging.

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Disclosure statement

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