Pediatric Medication Safety: Analyses from the MEDMARX Medication Error Reporting System

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STRUCTURED ABSTRACT:

Purpose: To identify medications, situational characteristics, and patient characteristics that are associated with high-harm medication errors in selected pediatric conditions that pose a high healthcare burden and to systematically explore the causes of these errors.

Scope: Medication errors are common and result in substantial morbidity and mortality. Children may be at increased risk for medication errors compared with adults. This study involved medication error reports originating from participating facilities in all 50 US states.

Methods: We performed cross-sectional, clustered analyses of MEDMARX, an anonymous, de-identified, national database that health systems use to collect, report, and share medication errors. All MEDMARX error reports utilize a standard taxonomy and provide information regarding the error's type, timing, location, involved phase of care, level of harm, causes of and contributing factors to the error and the medication involved.

Results: Across the five sub-projects (ADHD medications, cardiovascular medications, vaccines, antidepressants, NICU), there were fewer reports of errors that were associated with harm than reports of errors that were not associated with harm. Error attributes were similar between harmful and non-harmful errors. Several systems-focused themes (e.g., the need for careful handling of look-alike/sound-alike medications) emerged from analyses of error causes.

Key Words: medication errors, pediatrics, attention deficit hyperactivity disorder, vaccines, neonatal intensive care unit, cardiovascular agents, antidepressive agents

PURPOSE

The overall goal of this Pediatric Medication Safety project was to advance knowledge of pediatric medication errors by identifying which medications, children, and care situations are associated with high-harm medication errors among high-healthcare-burden pediatric conditions as well as to systematically explore the causes of these errors. These analyses serve as a tool to identify areas and medications in need of targeted interventions for reducing errors. Via an established research partnership between the United States Pharmacopeia (USP) and the Johns Hopkins University, the MEDMARX creators and experienced patient safety researchers collaborated to scientifically examine pediatric medication errors and their risks.

Focusing on high-healthcare-burden pediatric conditions, the Specific Aims of this project were

Specific Aim #1: To examine which types of medications and which children are associated with reported harmful and near-harmful medication errors.

Hypothesis: The types of medications and children associated with these medication errors will not vary by high-healthcare-burden pediatric conditions.

Specific Aim #2: To examine whether the causes of 'no-harm' medication errors are the same as those errors that are harmful.

Hypothesis: The causes and contributing factors for medication errors not resulting in harm will be the same as those for harmful medication errors.

This project provides one of the first intimate and national looks into pediatric medication errors. Equally important, this project was one of the first comprehensive evaluations of pediatric medication errors in ambulatory settings. The products of this research, we hope, will be directly useful in developing targeted solutions and policies to prevent harm to children from medication errors.

SCOPE

Background & Context: Medication errors are common and result in substantial morbidity and mortality. Children may be at increased risk for harmful (and non-harmful) medication errors compared with adults. The etiology of this increased risk is multifactorial and includes the complexities of weight-based dosing, the wide variety of available pediatric formulations, uncertainty regarding when to transition from pediatric to adult dosing, increased prevalence of off-label medication usage in children, and children's diminished ability to effectively communicate the earliest signs of medication toxicity. Although a growing body of literature is beginning to characterize medication errors, the majority of this literature focuses on adults in inpatient settings. Child-focused evaluations, in particular in outpatient settings, have been limited to date.

Setting: This study involved medication error reports originating from participating facilities in all 50 US states. Error reporting sites were primarily hospital affiliated, such that freestanding ambulatory practices were underrepresented in the ambulatory data.

Participants: Medication errors are reported to the MEDMARX database by a variety of provider types across a variety of settings. Nurses, pharmacists, physicians, and other health professionals at participating locations are permitted to submit medication error reports to MEDMARX.

Incidence & Prevalence: MEDMARX data are numerator data only. That is, they capture reported medication errors but do not capture the overall number of medication uses (i.e., the denominator). As such, MEDMARX data cannot be used to calculate the incidence or prevalence of medication errors. Similarly, the true incidence/prevalence of medication errors in participating sites is unknown; MEDMARX captures only the fraction of such errors that are reported.

METHODS

We conducted five sub-studies as part of the overall study. Each sub-study involved similar methods, which are described below.

Study design: Our studies were cross-sectional analyses of a national medication error reporting database.

Data source: Introduced in 1998, United States Pharmacopeia's MEDMARX is an anonymous, de-identified, voluntary national, internet-accessible database that hospitals and healthcare systems use to collect, report, track, and share adverse drug reactions and medication errors in a standardized format. Errors are identified through spontaneous reporting, retrospective chart review, and computer triggers; data are entered by physicians, nurses, pharmacists, and ancillary providers. Hospitals and healthcare systems subscribe to MEDMARX on an annual basis; 762 hospitals were subscribers as of January 2005 and represented all 50 states. Subscribers can access de-identified records from a national database of nearly 1.4 million medication error reports for benchmarking purposes. Formerly, and throughout the conduct of this study, MEDMARX was operated by the US Pharmacopeia; MEDMARX is presently managed by Quantros (http://www.quantros.com/medmarx.htm).

All MEDMARX error reports utilize a standard taxonomy and provide information regarding the error's timing, location, involved phase of care, degree of harm, cause of the error, medication involved, type of error, contributing factors, staff members involved, and actions taken as a result as well as information on the facility in which the error occurred. Some data fields within the error reports are single-pick lists, and some are multi-pick lists; the latter allow users to enter multiple answers, whereas the former insist on a single selection. There are also free text fields, allowing users to more fully describe errors.

Measures: The key measure of error harmfulness is known as 'error category' in the MEDMARX taxonomy. Medication error reports each included a National Coordinating Council

for Medication Error Reporting and Prevention Index for Categorizing Medication Errors category designation (A–I) depending on the severity of the error. Category A errors involved circumstances or events that may have the capacity to cause error, but no error occurred (i.e., "near misses"). Categories B through D errors involved situations in which an error did occur, but no harm resulted. Categories E through H errors not only occurred and reached the patient but also caused harm. Category I errors were those resulting in a patient death.

Limitations: MEDMARX data have a number of limitations. MEDMARX data do not include information regarding the total number of medication uses. Therefore, calculation of error incidence rates is not possible. Additionally, MEDMARX data are entered by a variety of clinical staff and are not verified for accuracy. Interreporter reliability of the MEDMARX data has been confirmed for error category but not for other data elements. As a voluntary reporting system, MEDMARX likely represents a substantial underreporting of true error incidence. With no 'gold standard,' there is no way to quantify this underreporting. Error reporting may be biased such that certain types of errors (e.g., more harmful ones) may be more likely to be reported than other errors. As a result, the relative frequencies of error characteristics reflect only those in reported errors, not in all errors that occurred. In addition, MEDMARX data provide limited information on the type of adverse events and harm that resulted from the reported errors and no information on the psychological impact of reported errors on patients and families. Finally, MEDMARX participants do not comprise a nationally representative sample of entities providing ambulatory medical care to children. In particular, hospital-based or affiliated ambulatory sites are overrepresented in MEDMARX compared with free-standing, office-based practices. Despite these limitations, MEDMARX is the largest medication error reporting database in the United States and sheds light on medication errors that would be difficult to analyze in smaller samples.

RESULTS

The principal findings and outcomes will be summarized for the five sub-projects.

Project 1: Attention deficit hyperactivity disorder (ADHD) agents

We analyzed 361 ADHD-related medication error reports involving the ambulatory care of children from 2003 to 2005. Most reported errors reached patients, but few were harmful.

- The majority of errors involved methylphenidate (MPH) or amphetamine/ dextroamphetamine (A/D).
- MPH errors were more likely to involve prescribing and less likely to involve dispensing.
- A/D errors were more likely to originate with pharmacy staff and involve wrong dosage forms. MPH errors were more likely to originate with physicians and involve prescribing problems.

Project 2: Vaccines

Using the "5 Rights" framework (right medication, patient, dose, time, and route), we found that error types were predictable, mainly due to vaccine- or patient-related human factors.

- Wrong-vaccine errors were more common among vaccines with "look-alike/sound-alike" pairs than among those without.
- Wrong-dose errors were more common among vaccines with weight-based dosing compared with those with standardized dosing.
- Wrong-time errors were more common among scheduled vaccines than among seasonal and intermittent ones.
- Wrong-route errors were rare but may be more common among subcutaneous vaccines (less commonly used route) compared with intramuscular vaccines (more commonly used route).
- Wrong-patient errors were also uncommon and often involved sibling-sibling confusion.

Although few vaccination errors were harmful, the damage done to the provider-patient relationship by vaccination errors may be substantial. This is of particular concern in an era of increasing parental scrutiny of the safety of vaccines.

Project 3: Cardiovascular agents

In total, 893 cardiovascular products were implicated in 821 reports. Error reports most frequently involved diuretics, followed by antihypertensive agents, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, β-adrenergic receptor blockers, digoxin, and calcium channel blockers. The most frequently reported agents were consistent across facility types and error locations. The largest proportions of harmful reports were associated with nesiritide, calcium channel blockers, indomethacin, milrinone, antiarrhythmic agents, and digoxin. Although diuretics were cited most frequently, only 4% of reports were classified as harmful. There were no differences in the proportions of harmful reports by drug class after accounting for statistical clustering by facility. Fifty percent of all error reports involved infants <1 year of age, with 90% involving infants <6 months of age. The age distribution of harmful reports was similar to that of the total group of cardiovascular medication error reports (harmful + non-harmful). There was no difference in the frequency of harmful reports according to age in the clustered analysis. However, all harmful reports except one involved children <9 years of age.

Project 4: Neonatal intensive care unit (NICU)

In total, 6749 NICU medication error reports were submitted by 163 facilities. The majority of errors were Category C (the error reached the patient but did not result in harm). Administering errors were involved in 48% of all medication error reports. Improper dose and quantity of medication, defined as any dose or strength of medication that differs from the prescribed order (including incorrect dispensing of medication), was involved in 27% of medication errors. Failure to administer an ordered dose (omission error) and incorrect administration time of medication (wrong time) yielded 19% and 18% of the medication errors, respectively. Of the reports that provided information regarding patient outcomes, the

majority indicated that the patient needed increased monitoring or hospitalization (41%), drug therapy changed or initiated (32%), or increased diagnostic testing (22%). In total, 342 different medications were identified by the error reports. Institute for Safe Medication Practices (ISMP) High-Alert Medications were cited in 22% reports. Total parenteral nutrition (TPN) was the most frequently cited ISMP High-Alert Medication. The most frequently cited drugs overall were gentamicin (8.8%), ampicillin (5.6%), TPN (5.5%), and fat emulsions (4.7%). Factors that were more likely to result in harmful medication errors included use of ISMP High-Alert Medications, errors occurring in the prescribing phase of medication processing, or equipment/delivery device failures.

Project 5: Antidepressive agents

Of the 451 error reports identified, 95% reached the patient, with 6.4% reaching the patient and necessitating increased monitoring and/or treatment. Seventy-seven percent involved medications being used off label. Thirty-three percent of errors cited administering as the cause of the error, 30% cited dispensing, 28% cited transcribing, and 7.9% cited prescribing. The most commonly cited medications were sertraline (20%), bupropion (19%), fluoxetine (15%), and trazodone (11%). We found no statistically significant association between medication and reported patient harm; harmful errors involved significantly more administering errors (59% vs. 32%, $p = 0.023$), errors occurring in inpatient care (93% vs. 68%, $p = 0.012$), and extra doses of medication (31% vs. 10%, $p = 0.025$) compared with non-harmful errors. Outpatient errors involved significantly more dispensing errors ($p < 0.001$) and more errors due to inaccurate or omitted transcription ($p < 0.001$) compared with inpatient errors. Family notification of medication errors was reported in only 12% of errors.

Discussion:

The discussion will be framed around the five sub-projects.

Project 1: Attention deficit hyperactivity disorder (ADHD) agents

Improper dose was the most common error type observed in our study, consistent with previous studies of pediatric medication errors. Improper dose was a significantly more common error type with MPH than with A/D. This disparity may have resulted from the fact that dosing for MPH is often weight based, whereas A/D dosing is standardized. Another possible explanation is that MPH tablets are sized such that more than one tablet is often needed for a single dose, whereas most doses of A/D in the standard range can be accommodated with a single pill, potentially reducing the likelihood of improper dosing.

Wrong dosage form was the second most common error type in our study. Provision of the wrong dosage form of a medication is particularly likely when multiple formulations of the same medication have names that sound or look similar. Medication errors associated with look-alike/sound-alike medication names have been identified by the World Health Organization Collaborating Centre for Patient Safety as one of nine target areas for "Life-Saving Patient Safety Solutions." Although confusion of dosage forms with ADHD-related medications is unlikely to be hazardous to health, it may result in increased side effects, reflecting long-acting formulations inadvertently used multiple times per day, or decreased efficacy because of short-acting formulations inadvertently used once daily.

Medications with suffixes (for example, XR, XL, LA) that denote different formulations are particularly susceptible to dosage-form errors. Indeed, many often-confused medication pairs involve use of a single base name and multiple suffixes. In one study of hospitalized patients, failure to specify the controlled-release formulation was the most common cause of prescribing errors involving medication-dosage forms. Our study suggests that wrong-dosage forms, especially among medications with suffixes denoting varying formulations, are one of the most common types of medication errors involving ADHD-related medications.

Project 2: Vaccines

Administration of the wrong vaccine was a commonly reported error type in our analysis and the most commonly identified error type in two analyses of the Vaccine Adverse Event Reporting System (VAERS) database. Inadvertent substitution of one vaccine for another has been reported repeatedly in the literature and usually involves vaccines with generic or trade names that look or sound alike. Look-alike/sound-alike errors have been reported for Tdap/ DTaP (for which brand names, Adacel and Daptacel, also look and sound alike) and Td/DT. Non-tetanus vaccines are also implicated in this error type, including both generic (e.g., pneumococcal conjugate/pneumococcal polysaccharide) and trade (Recombivax HB/COMVAX) name confusion. Standardizing vaccine nomenclature has been proposed as one means of reducing the incidence of wrong vaccination errors. Tall man lettering has also been shown to reduce confusion between medications with similar-appearing names (e.g., TWINrix, INFANrix, and KINrix), though existing generic vaccine nomenclature confounds this strategy in some cases by the use of capital letters to signify the concentration of included components (e.g., Tdap vs. DTaP). Standardized nomenclature and tall man lettering have been endorsed by the Institute for Safe Medication Practices and the Pediatric Pharmacy Advocacy Group.

Similar-appearing packaging is another root cause of wrong vaccine errors. In addition to standardizing vaccine packaging and labeling, barcodes have been proposed as one potential solution to confusing packaging. Such strategies, similar to those aimed at reducing look-alike/ sound-alike confusion, would require the cooperation of major vaccine manufactures and regulatory agencies, such as the US Food and Drug Administration, as well as possibly requiring the purchase of additional barcode scanners by hospitals and ambulatory providers in a time of increasing budget crises Unfortunately, there is no current agency or organization empowered to oversee these needed patient safety fixes.

In our study, wrong-time errors represented a commonly reported error type. This finding is concordant with a British study in which 61% of all reported errors were “out of schedule,” “outside the indicated age,” or “inappropriate interval.” Wrong-time vaccination errors involve

deviations from the recommended vaccination schedule and include errors of omission and commission. Errors of commission, in turn, can involve giving a vaccine too early for patient age or by recommended interval or when it is no longer indicated, based on patient age or prior receipt of vaccinations. One study using this framework to evaluate invalid vaccination doses found that each of these three types of errors of commission were equally common. These errors falsely inflate population vaccination rates, because the total number of vaccines received by a child may be adequate, but, when minimum spacing and recommended vaccine timing is considered, true population-'appropriate' vaccination rates are substantially lower. Although under vaccination is likely the greater public health problem, such errors are less likely to be reported than are errors of commission, which result in extra vaccination. In one study of nationally representative US data, extra vaccination occurred in 21% of young children.

Although the underlying causes of wrong-time errors in our data could not be determined, one root cause of such errors is inadequate vaccination records. With the complexity of the recommended vaccination schedule continually increasing, the importance of accurate vaccination recordkeeping is magnified. Many practices, cities, and states have adopted electronic vaccination records and registries. Sixty-five percent of US children under age 6 participate in large-scale, electronic immunization information systems; unfortunately, even for participating children, data are often incomplete and not reported in a timely fashion. Future studies should determine the impact of these electronic records on the vaccination status of children and wrong-time vaccination errors.

Project 3: Cardiovascular agents

Diuretics and antihypertensive agents were reported most commonly. Harmful errors occurred with all cardiovascular drug classes. Of the medications reported, nesiritide, calcium channel blockers, indomethacin, milrinone, digoxin, and antiarrhythmic agents had the largest proportions of harmful reports, although differences between drug classes were not statistically significant and numbers were small. No deaths were reported, but the most morbid error resulted in cardiac arrest and involved an antiarrhythmic agent, milrinone, and digoxin. In

addition, errors involving infants were reported more frequently and accounted for 50% of total errors; most of these errors involved patients <6 months of age. There were no significant differences in the proportions of harmful errors according to age. Medication administration was implicated most frequently, with improper dosing being the most frequently cited error type for both harmful and non-harmful errors.

Project 4: Neonatal intensive care unit (NICU)

This study is both the largest analysis of NICU medication errors to date and the first to demonstrate that use of ISMP High-Alert Medications is a risk factor for harm in the NICU. Additional risk factors for harm also emerged in this study and include errors that begin in the prescribing phase of medication use and failures in equipment and delivery devices. Collectively, these factors have begun to lay the groundwork for a risk profile for harmful medication errors in the NICU. Our findings are also consistent with previous studies that have highlighted anti-infective, analgesic/sedative, and electrolytic/fluid agents as the most common drugs involved in pediatric, and now specifically NICU, medication errors. Our results likely reflect the frequent use of these medications in the NICU.

Our study has identified several targets for intervention in preventing harmful medication errors in the NICU. First, more work on the delivery and monitoring of ISMP High-Alert Medications, as well as on the most frequently cited medications in NICU error reports, such as aminoglycosides and opiates, is needed. Second, our study indicates that the current push for installing computerized physician order entry (CPOE) systems nationwide would be beneficial in preventing harmful medication errors in the NICU. However, because over half the errors occurred at the administering stage of medication processing, other interventions, such as the smart pump, would be useful to reduce these errors. Yet, caution must be exercised when introducing these devices in the NICU. As shown in this study, faulty equipment and delivery devices for medication administration were associated with harm. Strategies to help reduce this potential for harm need to be explored and can include techniques such as direct

observational analyses and simulations. Our data suggest that, by targeting these risk factors for harm in the NICU, a significant number of errors that occur in this clinical setting could be reduced.

Project 5: Antidepressive agents

Our examination of inpatient antidepressant medication errors echoes previous inpatient psychotropic medication error findings: the majority of these medication errors do not cause lasting harm to the patient; wrong dose and omitted medication error types are common; human performance deficits are a common error cause; and administration and transcription errors are common error nodes. We did not find a majority of prescribing errors as previously cited, likely because voluntary error reporting is driven primarily by nurses and pharmacists, whereas previous studies have used chart reviews. Our outpatient data have only limited literature comparison. In our study, improper dose rates were higher in the outpatient setting, as were wrong-patient errors. More than half of outpatient wrong-patient errors were due to name confusion at the pharmacist level due to relatives with similar names. This is an area almost unique to the outpatient setting and should be highlighted to providers, patients, and their families.

Not surprisingly, a large majority of reported pediatric antidepressant medication errors occurred during off-label usage. Based on the NIMH listings of FDA safety and efficacy studies, only five antidepressants (clomipramine, fluvoxamine, doxepin, imipramine, and sertraline) are approved for use in patients younger than 18 years of age. Our data serve as another call for action to federal regulators and pharmaceutical companies to rigorously test the safety and efficacy of these medications in pediatric populations, as off-label usages comprised 77% of the errors cited in this database. It is unknown to what extent lack of clear pediatric dosing and indication guidance contributes to medication errors for these medications when used off label.

Our analyses provide a starting point for researchers and policymakers interested in improving the safety of antidepressant use in children. Manufacturers need to be aware of avoiding

similar naming strategies, such as bupropion extended-release (Wellbutrin XL®) and bupropion sustained-release (Wellbutrin SR®) (GlaxoSmithKline, Middlesex, UK). Inpatient systems solutions should be devoted more toward transcribing and administering problems, whereas outpatient solutions need to increase focus on correct patient identification and dispensing. Overall, more study on outpatient antidepressant errors is needed to shed light on this large source of ADEs that has been minimally addressed by the current literature. The rapidly expanding base of prescribers of pediatric antidepressants demands more careful examination of risks and preventive strategies for errors as well as awareness of the potential for errors in the prescribing of these medications.

Conclusions:

Harmful pediatric medication errors were relatively infrequently reported in the MEDMARX data. Nonetheless, our hypothesis that non-harmful medication errors would have similar characteristics to harmful ones was generally supported by the data. This suggests that, similar to the aviation industry's examination of "near-miss" events, the medical and pharmaceutical industries should consider studying non-harmful medication errors, of which many more are reported, in order to better understand and prevent harmful medication errors. In addition, we found that the same types of system failures that plague inpatient medical settings (e.g., failure to discriminate between two look-alike/sound-alike medications) are present in outpatient settings. Indeed, remedying these system failures in outpatient settings is likely more complex than doing so in inpatient ones, because there is no single overlying structure across which to implement system changes as there might be within an inpatient setting.

Significance & Implications:

Our research suggests that no single organization or entity has sufficient reach to single-handedly reduce the burden of medication errors in pediatric populations. Regulatory agencies (e.g., the Food and Drug Administration, The Joint Commission); advocacy organizations (e.g., the Institute for Safe Medication Practices); physician, pharmacist, and nursing organizations; retail pharmacies; and families and patients would all need to make significant, coordinated efforts in order to begin to reduce the burden of medication errors in children. We believe this effort is underway but in its infancy. Hopefully, data such as those generated by our research and the work of others will provide the necessary scientific and epidemiological underpinnings to allow the interested participants delineated above to take evidence-based, system-focused steps toward increasing the safety of medication use for all children.

INCLUSION OF AHRQ PRIORITY POPULATIONS

Each of the studies described above focused exclusively on children, an AHRQ Priority Population. Furthermore, several of the studies focused, though indirectly, on children with special healthcare needs, as evidence by their need for the chronic medications under study (e.g., ADHD and antidepressive or cardiovascular agents).

LIST OF PUBLICATIONS AND PRODUCTS

1. Bundy DG, Rinke ML, Shore AD, Hicks RW, Morlock LL, Miller MR. Medication errors in the ambulatory treatment of pediatric attention deficit hyperactivity disorder. *Jt Comm J Qual Patient Saf*. 2008 Sep;34(9):552-9, 497.

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4. Stavroudis TA, Shore AD, Morlock L, Hicks RW, Bundy DG, Miller MR. NICU medication errors: Identifying a risk profile for medication errors in the Neonatal Intensive Care Unit. In press at *J Perinatol*.

5. Rinke ML, Bundy DG, Shore AD, Colantuoni E, Morlock LL, Miller MR. Pediatric antidepressant medication errors in a national error reporting database. In press at *J Dev Behav Pediatr*.