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Outpatient Insulin-related Adverse Events Due to Mix-up Errors: Findings from Two National Surveillance Systems, United States, 2012–2017

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Abstract

Purpose: We used data from two public health surveillance systems for national estimates and detailed descriptions of insulin mix-up errors resulting in emergency department (ED) visits and other serious adverse events to help inform prevention efforts.

Methods: ED visits involving patients seeking care for insulin medication errors collected by the NEISS-CADES project in 2012–2017 and voluntary reports of serious insulin medication errors submitted to the U.S. Food and Drug Administration (FDA) in 2016–2017 were analyzed. National estimates of insulin product prescriptions dispensed from retail pharmacies were obtained from IQVIA National Prescription Audit.

Results: Between 2012 and 2017, based on 514 NEISS-CADES cases, there were an estimated 5,636 (95% CI, 4,143–7,128) ED visits annually for insulin mix-up errors; overall, over three-quarters (77.5%; 95% CI, 71.6%-83.3%) involved taking rapid-acting instead of long-acting

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insulin. Between 2012 and 2017, the proportion of mix-up errors among all estimated ED visits for all insulin errors decreased by 60%; concurrently, the proportion of pens among all insulin package types dispensed increased by 50%. Among 58 voluntary reports submitted to FAERS, over one-half (56.9%) of cases involved taking rapid- instead of long-acting insulin. Among 27 cases with documented contributing factors, approximatley one-half involved patients having difficulty differentiating products.

Conclusions: Among all ED visits for insulin errors collected by NEISS-CADES in 2012–2017, the proportion involving mix-up errors has declined. Continued reductions may require additional prevention strategies, including improving insulin distinctiveness, particularly for rapid- vs. long-acting insulins. Ongoing national surveillance is important for identifying the impact of interventions.

Keywords

Insulin; Medication Errors; Drug-related Side Effects and Adverse Reactions; Hypoglycemia; Health Literacy; Drug Packaging

INTRODUCTION

Insulin is a cornerstone of type 1 diabetes mellitus (DM) treatment and is often employed in the treatment of patients with type 2 DM. Insulin therapy remains one of the most challenging aspects of DM medical management due to complexities in dosing and administration, dependency on routine blood glucose monitoring and patterns of food intake, as well as the associated risks of hypoglycemia, which in its most serious form can be fatal.[1–5]

Insulin is also one of the most common medications involved in medication errors and correct administration of insulin in outpatient settings requires adequate levels of health literacy and numeracy.[1–6] Often, two different insulin products with different onsets and durations of action are used concurrently to manage diabetes adequately. In addition, patients use different brands of insulin products, which can have different container labeling and product package characteristics. We have previously identified confusion among insulin products as a common contributor to insulin medication errors resulting in emergency department (ED) visits for hypoglycemia.[6] Using data from the National Electronic Injury Surveillance System–Cooperative Adverse Drug Event Surveillance (NEISS-CADES) project and the U.S. Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) we sought to (1) calculate more recent national estimates of insulin mix-up errors resulting in ED visits and hospitalizations, (2) identify the type of insulin mix-up errors resulting in serious adverse drug events (ADEs) to inform prevention efforts, and (3) place insulin mix-up errors in the context of changes in insulin use.

METHODS

Definitions and Terminology

Cases of insulin mix-up errors included accidental administration of a different insulin product than intended (i.e., “product mix-up error”), or accidental adminstration of a

different insulin dosage than intended (i.e., “dosage mix-up”). An example of a “product mix-up” case is a patient who intended to take their long-acting insulin but administered their short-acting insulin instead. An example of a “dosage mix-up” case is a patient who inadvertently administered their short-acting insulin at the dose prescribed for their long-acting insulin (Supplementary Table S1). We excluded insulin errors reported as unintentional administration of the wrong number of insulin units unrelated to product mix-ups, intentional injection of additional units that were not prescribed, insulin pump-related errors, or meal-related errors.[6] We also excluded cases involving non-insulin medications (e.g., mix-up between insulin and exenatide) and cases with insufficient evidence to determine if a mix-up error occurred. In addition, we excluded cases that described the intentional use of the incorrect insulin product. For example, a report describing a patient instructed to change from NPH insulin to insulin glargine, but who intentionally continued to administer NPH insulin to use up their remaining supply, would be excluded because replacement of one insulin for the other was intentional.

In this manuscript, “insulin product type” refers to the pharmacologic category of a given insulin product (“long-acting”, “rapid-acting”, “short-acting”, “intermediate-acting”, or “insulin mix”). “Package type” refers to the container in which the insulin is dispensed (vial or pre-filled pen). Insulin product type categories are described in Table 1.

National Estimates (National Electronic Injury Surveillance System–Cooperative Adverse Drug Event Surveillance, NEISS-CADES)

We estimated the numbers of U.S. ED visits and hospitalizations for insulin mix-up errors between January 1, 2012 and December 31, 2017 based on data from the 57 to 63 hospitals participating in the NEISS-CADES project, a nationally-representative, size-stratified probability sample of hospitals (excluding psychiatric and penal institutions) in the United States (U.S.) and its territories with a minimum of 6 beds and a 24-hour emergency department. The sample includes separate strata for very large, large, medium, and small hospitals, defined by the number of annual ED visits per hospital, and children’s hospitals. NEISS-CADES collects over 20,000 adverse drug event cases annually and has been used for over a decade to provide national estimates of drug-related harm.[7–12] As described previously, trained abstractors at each hospital review clinical records of every ED visit to identify physician-diagnosed ADEs, and report the medications implicated in the adverse event as well as concurrent medications and relevant preceding events documented in the medical record.[12,13] Clinical manifestations are coded according to the Medical Dictionary for Regulatory Activities (MedDRA), version 9.1. All 2012–2017 insulin cases with MedDRA preferred terms (PTs) for medication errors were identified and cases with PTs “*Wrong drug administered”* or “*Incorrect dose administered”* were reviewed to identify and categorize cases meeting the definition of mix-up errors.

Case Reports (Food and Drug Administration Adverse Event Reporting System, FAERS)

We summarized cases of insulin mix-up errors reported between January 1, 2016 through December 31, 2017 from FAERS, the national spontaneous surveillance system for post-marketing adverse events and medication errors associated with U.S.-marketed drugs and therapeutic biologic products.[14] We limited our search of FAERS to a 2-year timeframe

as product design and labeling may change over time and this search was intended to provide qualitative root cause data for recent cases. FDA defines a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of a healthcare provider, patient, or consumer; a medication error may or may not result in an adverse event.[15] We restricted our search of FAERS to U.S. cases of medication errors that resulted in serious outcomes (e.g., hospitalization, disability, life-threatening event, or death)[16] and excluded cases that occurred in inpatient settings (i.e., error occurred during hospitalization). We reviewed all 2016–2017 FAERS serious cases that reported insulin as the primary suspect and were coded with a Preferred Term from the Standardized MedDRA Query "Medication Errors (narrow)" (MedDRA version 21.0). We then categorized cases that met the case definition of insulin mix-up errors, and determined the types of insulins involved in the mix-up, package type, and root cause or contributing factors stated by the reporter. We used the National Coordinating Council for Medication Error Reporting and Prevention taxonomy to guide categorization of causes and contributing factors for mix-up errors.[17]

Prescription Data

To assess changes in numbers and types of insulin products used from 2012 to 2017, we obtained insulin prescription dispensing data during that time period from the IQVIA National Prescription Audit (NPA), which measures the "retail outflow" of prescriptions, or the rate at which drugs move out of retail pharmacies, mail service houses, or long-term care facilities into the hands of U.S. consumers via official prescriptions dispensed by pharmacies. Data for the NPA audit is a national level estimate of the drug activity from retail pharmacies. The NPA receives over 3.5 billion prescription claims per year, captured from a sample of the universe of approximately 59,400 U.S. pharmacies. The pharmacies in the database account for most retail pharmacies and represent nearly 88% of retail prescriptions dispensed nationwide.

Statistical Analyses

Each NEISS-CADES case is weighted based on inverse probability of selection, adjusted for non-response and hospital non-participation, and post-stratified to account for changes in the number of U.S. ED visits each year.[13] National estimates and proportions of ED visits and hospitalizations for insulin errors and corresponding 95% confidence intervals (CIs) were calculated using the SURVEYMEANS procedure in SAS (version 9.4, SAS Institute, Cary, NC) to account for the sample weights and complex sample design. Estimates and their corresponding confidence limits calculated from NEISS-CADES were divided by 6 to obtain average annual estimates and CIs. Estimates based on small numbers of cases (<20) or with a coefficient of variation greater than 30% were considered statistically unstable and are noted in the tables.

Institutional Review

Data collection in NEISS-CADES and FAERS has been deemed public health surveillance activities and did not require IRB approval.[18]

RESULTS

Between 2012 and 2017, based on the data from hospitals participating in the NEISS-CADES project, we identified 514 cases involving insulin mix-up errors. Based on these 514 cases, there were an estimated annual average of 5,636 ED visits (95% CI, 4,185–7,170 ED visits) involving insulin mix-up errors, accounting for 15.7% (95% CI, 12.2%-19.2%) of the estimated 35,869 (95% CI, 25,588–46,150) ED visits for all insulin medication errors annually (Table 2). ED visits for mix up-errors were nearly evenly divided between patients 65 years of age or older (41.3%; 95% CI 36.1%-46.6%) and patients 45–64 years of age (44.2%; 95% CI, 39.7%-48.7%). A lower proportion of estimated ED visits for insulin mix-up errors resulted in hospitalization (13.8%; 95% CI, 8.6%-18.9%) compared with visits involving other types of insulin errors (26.3%; 95% CI, 20.9%-31.7%) (Table 2).

In almost all (96.4%) ED visits for insulin mix-up errors, two prescribed insulin products were documented and, in an estimated 3.6% of ED visits, three or more insulin products were documented (Table 3). Rapid-acting and long-acting insulins were the most commonly involved products in ED visits for insulin mix-up errors, and an estimated 22.7% (95% CI, 17.2%-28.1%) of ED visits documented concurrent oral diabetes medication use by the patient. An estimated two-fifths (41.6%) of ED visits for insulin mix-up errors involved hypoglycemia, while the remaining cases did not specify if hypoglycemia occurred. Among cases for which location of insulin administration was documented, most (70.5%) insulin mix-up errors occurred at home. In most ED visits (98.3%; 95% CI, 97.2%-99.4%), it was not documented whether insulin was being administered from a vial or a pre-filled pen.

Of 514 cases of insulin mix-up errors, 499 cases were “product mix-up” cases (i.e., one insulin was intended to be administered, but another was administered instead), and 11 cases were “dosage mix-up” cases (i.e., two insulins were administered, but the doses were switched). Among the 499 “product mix-up” cases, rapid-acting insulin (81.0%; 95% CI, 75.1%-86.9%) and short-acting insulin (9.2%; 95% CI, 5.4%-13.1%) were the most common insulin products mistakenly administered (Supplementary Table S2). The most common mix-up among “product mix-up” cases was administering rapid-acting insulin instead of long-acting insulin, occurring in an estimated 77.4% (95% CI, 71.5%-83.4%) of ED visits for this case type, followed by administering short-acting insulin instead of long-acting insulin (7.4%; 95% CI, 4.3%-10.6%). Among the 11 “dosage mix-up” cases, the most common wrong combination involved mix-up dosing when administering rapid-acting insulin and long-acting insulin, accounting for all but 1 case. Overall, among cases where the wrong combination was taken (both “product mix-up” and “dosage mix-up” cases), an estimated 77.5% (95% CI, 71.6%-83.3%) of ED visits involved rapid-acting and long-acting combinations. There were 4 additional cases in which a mix-up error occurred, but it was unclear which insulin was intended versus administered; all of these cases involved rapid- and long-acting insulins.

The estimated proportion of ED visits for all types of insulin errors that involved a mix-up decreased by 60.5%, from 23.8% (95% CI, 17.1%-30.4%) in 2012 to 9.4% (95% CI, 6.3%-12.4%) in 2017 (Figure). Concurrently, there was a 50% increase in the estimated

proportion of dispensed prescriptions for insulin pre-filled pens and a 33% decrease in the estimated proportion of dispensed prescriptions for insulin vials.

From FAERS, we identified 58 U.S. serious insulin mix-up errors cases in 2016–2017 that described events in which patients administered the incorrect insulin instead of their intended or expected insulin, including scenarios resulting from prescribing or dispensing errors. Most of the cases (41 of 58; 70.7%) involved rapid-acting insulin, with 56.9% (33 of 58) involving administration of rapid-acting instead of long-acting insulin. Among cases where contributing factors were reported, approximately one-half of those cases (14 of 27) involved difficulty differentiating between products, including confusion due to similarities in product packaging or labeling (Table 4). Among 49 cases where insulin package type was documented, most cases (85.7%) involved pre-filled pens. Nearly three-quarters (70.7%) of the 58 cases documented hypoglycemia.

DISCUSSION

Based on data from two nationwide surveillance systems, this analysis characterizes insulin mix-up errors from 2012–2017 and highlights prevention opportunities. Insulin mix-up errors were a relatively small proportion (15.7%) of all insulin ADE ED visits; however, considering insulin is used by millions of patients with diabetes[19] and that these types of errors are particularly amenable to prevention, understanding the burden of and contributing factors to these clinically significant adverse events is important. The FAERS data identified important contributing factors to mix-up errors, including difficulty distinguishing between insulin products based on appearance alone and misunderstanding the role of insulin product types in the therapeutic regimen, indicating potential opportunities for medication error prevention, including improved patient education in the short-term, and, over the long-term, modification of product packaging.

In the short-term, improving patient education, including incorporating content specifically targeted at improving patients' ability to correctly identify different products and comprehension of the insulin regimen, will be important. In 2017, there were approximately 50 different types of insulins (when accounting for product and package types) commercially available in the United States. Combination therapy with multiple daily injections of prandial and basal insulin products is the foundation for managing type 1 DM and an important therapeutic option for type 2 DM.[20] With so many products available and as treatment regimens change over time to optimize diabetes management, adhere to changing formularies, or for other reasons, continuously assessing inulin use patterns and educational materials to improve patients' understanding and implementation of their insulin regimens will be important.

There is substantial room for improvement in current diabetes treatment educational resources for incorporating best health literacy and numeracy principles.[21,22] An example of patient educational content that aims to emphasize differences between insulin product types with differing onsets of action and roles in the insulin treatment regimen was developed by the authors (AOC and HM), based on similar content found in Veterans Health Administration diabetes educational materials (Supplementary Figure S1). Low

health literacy is correlated with poor quality diabetes self-management and modifications to diabetes education tools that address health literacy issues have been shown to improve diabetes-related outcomes.[23–25] New educational materials should be evaluated for their impact on patients correctly identifying their insulin vials and pens, correctly timing insulin administration, and knowledge of strategies that can potentially minimize risk of mix-ups (e.g., storing prandial and basal insulins in different locations).

In the longer term, these study findings suggest an opportunity to engineer solutions for distinguishing insulin products in order to minimize risk of mix-ups, as relying solely on product names and remembering differences among insulin product types may not be sufficient. FDA requires human factors testing for all drug-device combination products (including insulin pens) prior to approval, to support that these products can be used by the intended users without serious use errors when used as intended. The data are reviewed to determine if changes to the product design or product labeling are needed to reduce the risk associated with use of the product.[26] When reviewing submissions for injectable diabetes medications, FDA currently considers, in addition to the insulin product's name, product differentiation issues. There are very limited data on the impact of different colors and labels of insulin vials and pens on the ability distinguish among insulin products.[27,28] One small study suggested that distinguishing pens by changing the color of the full body of the pen aided patients in identifying the correct insulin product compared with pens that were a single color or partially colored.[21] However, among other study limitations, the patients in that study were not simulating actual use of insulin. Additionally, reliance on color alone to distinguish pens is likely less useful for patients with diabetes who have visual impairment, especially when manufacturers use similar colors on different insulin product types within their product lines and as the availability of contrasting colors becomes limited in growing product lines.

Despite known challenges inherent to insulin administration, once separated from packaging or labeling dispensed by the pharmacy, insulin pens and vials have no instructions for use on them, owing to space limitations. Labels on insulin pens have limited space and FDA already requires that these small labels include the proprietary and established names, product strength, expiration date, a lot or control number, and the manufacturer's information at minimum.[29] Although "Instructions for Use" documents are provided when insulin pens are dispensed in cartons and are available online, it is not clear if these are used by patients. Consideration could be given to creating space on insulin pens for a patient or caregiver to write their own instructions or add their own reminder for how to distinguish pens, without compromising the information currently required on labels (Supplementary Figures S2 and S3).

Insulin pre-filled pens have been purported to confer a lower risk of mix-ups compared with vials.[30] Between 2012 and 2017, there was a 50% increase in number of prescriptions dispensed of pre-filled pens and this study found an approximately 60% reduction in the proportion of ED visits for insulin medication errors that involved mix-up errors during the same time period (23.8% to 9.4%); however, whether or not the increased use of pens contributed to this reduction cannot be determined from these data. It will be important to continue to assess insulin pens for mix-up errors and other types of errors that can

result in adverse events, including those resulting from improper injection technique, as well as assessing the role of targeted patient education and improved product packaging in mitigating the burden of these errors.[31]

This study has limitations. First, the burden of insulin mix-up errors as errors is likely underestimated, as medication errors not resulting in ED visits are not included NEISS-CADES; FAERS relies on spontaneously reported data from the public, and identification of mix-up errors was limited to those resulting in serious adverse events. We could not determine whether the decline in mix-up errors is due to treatment guidelines increasingly recommending prandial insulin later in type 2 DM (13) or increased use of newer medications for type 2 DM (e.g., glucagon-like peptide -1 receptor agonists), and thus fewer patients on >1 type of insulin. It is possible that the decline in the proportion of insulin mix-up errors in NEISS-CADES was due to increased reporting of other types of insulin errors; however, additional evaluation of cases suggested this was not the reason. Detailed information regarding patient characteristics, including type 1 or type 2 diabetes diagnosis, and contributing factors for errors was not available for all cases. It is important that all medication errors, including those not resulting in an adverse event, be reported to FAERS, along with the circumstances leading to errors. Requiring manufacturers to report medication errors to FDA could provide more complete information on medication error burden and prevention efforts. This will be especially important for assessing the impact on insulin mix-up errors given increased use of non-insulin injectable diabetes products in outpatient settings.

CONCLUSION

The contribution of insulin mix-up errors to estimated ED visits for insulin errors appears to be declining, but additional prevention strategies should be explored to improve insulin product distinction, particularly for rapid- and long-acting insulin products. Ongoing national surveillance will be important for evaulating preventive interventions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Key Points:

- Insulin is a cornerstone of diabetes treatment, but a common cause of medication errors, including errors involving confusion (“mix-up”) between different insulin products.
- Between 2007–2017, among U.S. emergency department (ED) visits for all insulin medication errors, the estimated proportion of “mix-up” errors declined, coinciding with increased use of insulin pre-filled pens.
- Over three-quarters of insulin “mix-up” errors leading to ED visits involved patients unintentionally taking rapid-acting instead of long-acting insulin.
- The role of improved product packaging (distinctiveness among products) and targeted health literacy interventions (distinguishing between prandial and basal insulins) should be explored for further reductions on “mix-up” errors.

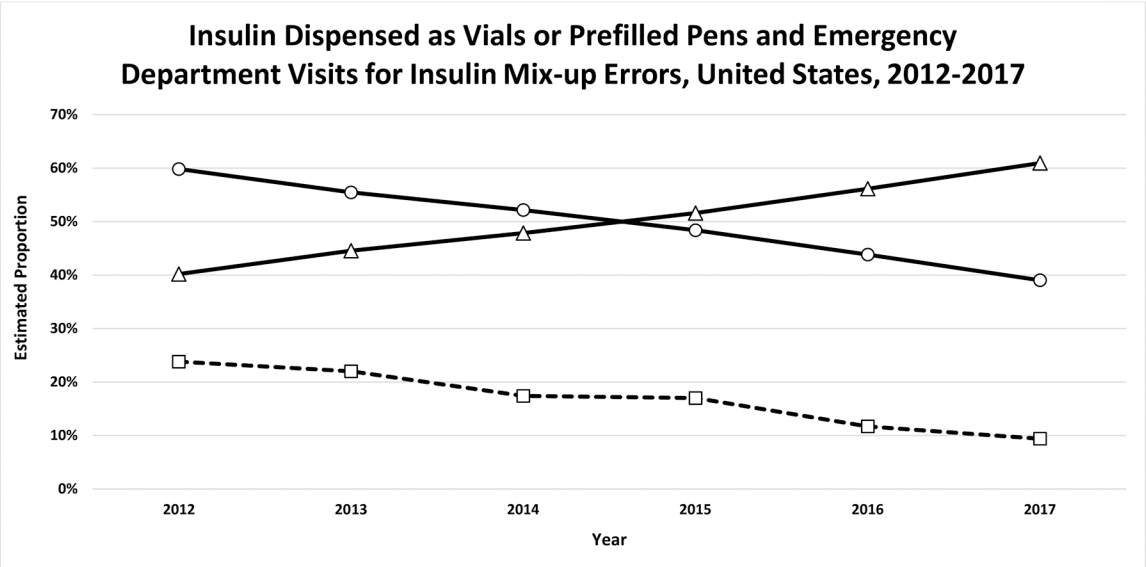

Figure.

Line chart displaying the annual projected (estimated) proportion of insulin vials (circles) and insulin pens (triangles) out of all nationally estimated insulin prescriptions dispensed through U.S. outpatient retail pharmacies (IQVIA National Prescription Audit, 2012–2017); and the annual estimated proportion of U.S. ED visits for insulin mix-up errors (squares) out of all U.S. ED visits for insulin adverse drug events involving medication errors (National Electronic Injury Surveillance System-Cooperative Adverse Drug Event Surveillance project, CDC, 2012–2017).

Squares = insulin mix-up errors; triangles = insulin prefilled pens; circles = insulin vial

Table 1.

Product Type Categorizations Used in Analysis of Insulin Mix-Up Error Cases

Insulin Product Type†	Included Products
Long-acting	Generic or brand-name degludec, detemir, glargine, or unspecified “long-acting” insulin products
Rapid-acting	Generic or brand-name aspart, glulisine, or lispro products
Short-acting	Generic or brand-name regular or unspecified “short-acting” insulin products
Intermediate-acting	Generic or brand-name NPH products
Insulin mix	Any combination product involving two insulin product types (e.g., “70/30”)
Not documented	Insulin products not otherwise described or specified

†“Short-acting” and “rapid-acting” insulin products are also collectively referred to as “prandial” insulins because both types are used to cover meals, and “long-acting” insulin products as “basal” insulins because they are used to cover the background release of glucose that is not associated with food intake.

Table 2.

Number of Cases and National Estimates of Emergency Department Visits for Insulin Adverse Events, by Patient Characteristics—United States, 2012–2017[†]

Patient Characteristics	ED Visits for Insulin Adverse Events								
	ED Visits with Mix-up Errors Documented[‡]			ED Visits With Other Types of Errors Documented			ED Visits Without Medication Errors Documented		
	Cases	Annual National Estimate		Cases	Annual National Estimate		Cases	Annual National Estimate	
	No.	No.	% (95% CI)	No.	No.	% (95% CI)	No.	No.	% (95% CI)
Age									
<18 years	8	~	~	53	383	1.3 (0.6–2.0)	147	1,223	1.2 (0.7–1.6)
18–44 years	75	751	13.3 (8.4–18.3)	746	6,369	21.1 (19.0–23.1)	1,796	19,196	18.3 (16.5–20.2)
45–64 years	233	2,489	44.2 (39.7–48.7)	1,378	11,992	39.7 (37.2–42.2)	3,516	37,223	35.5 (32.9–38.2)
≥65 years	198	2,330	41.3 (36.1–46.6)	1,287	11,490	38.0 (35.4–40.6)	4,157	47,112	45.0 (41.7–48.2)
Sex									
Female	268	3,138	55.7 (50.0–61.4)	1,590	14,027	46.4 (42.5–50.3)	4,723	52,040	49.7 (46.7–52.6)
Male	246	2,498	44.3 (38.6–50.0)	1,874	16,207	53.6 (49.7–57.5)	4,893	52,713	50.3 (47.4–53.3)
Discharge Disposition									
Admitted, transferred, or held for observation	74	776	13.8 (8.6–18.9)	934	7,955	26.3 (20.9–31.7)	3,912	40,559	38.7 (32.6–44.9)
Treated and released, or left against medical advice	440	4,860	86.2 (81.1–91.4)	2,530	22,279	73.7 (68.3–79.1)	5,704	64,194	61.3 (55.1–67.4)
Total	**514**	**5,636**	**4.0 (3.1–5.0)**	**3,464**	**30,234**	**21.5 (17.3–25.7)**	**9,616**	**104,753**	**74.5 (70.0–79.0)**

[†]Case counts and estimates from the National Electronic Injury Surveillance System - Cooperative Adverse Drug Event Surveillance (NEISS-CADES) project, CDC. Cases involving children found with or who accidently administered insulin without adult supervision are excluded (N=7).

[‡]Includes 1 case involving a product mix-up error and another type of insulin medication error, counted under the product mix-up column only.

Abbreviations: ED, emergency department; CI, confidence interval

Table 3.

Number of Cases and National Estimates of Emergency Department Visits Involving Insulin Mix-Up Errors, by Case Characteristics—United States, 2012–2017[†]

Case Characteristics	ED Visits for Insulin Mix-up Errors		
	Cases	Annual National Estimate	
	No.	No. (95% CI)	% (95% CI)
Number of Insulin Products [‡]			
1	0	~	~
2	493	5,432 (3,983–6,881)	96.4 (94.3–98.5)
≥3	21	203 (78–328)	3.6 (1.5–5.7)
Insulin Product Type [‡]			
Long-Acting	476	5,222 (3,763–6,681)	92.7 (89.6–95.8)
Rapid-Acting	443	4,805 (3,397–6,213)	85.3 (80.1–90.4)
Short-Acting (Regular)	51	629 (389–868)	11.2 (6.9–15.4)
Intermediate-Acting	8	~	~
Insulin Mix	10	~	~
Not documented	34	346 (204–489)	6.1 (3.5–8.8)
Other Diabetes Medications [‡]			
Biguanide (metformin)	89	1,059 (648–1,470)	18.8 (14.1–23.5)
Sulfonylurea	21	259 (125–393)	4.6 (2.8–6.3)
Dipeptidyl peptidase-4 inhibitor (gliptins)	14	~	~
Glucagon-like peptide-1 receptor agonists and Amylin analogs	5	~	~
SGLT2 inhibitors	3	~	~
Thiazolidinedione (glitazones)	2	~	~
Combination oral agents	5	~	~
No other diabetes medications documented	403	4,350 (3,204–5,495)	77.2 (71.7–82.6)
Hypoglycemia Documented [§]			
Yes	209	2,342 (1,658–3,027)	41.6 (34.6–48.5)
No	305	3,293 (2,289–4,298)	58.4 (51.5–65.4)
Location of Event			
Home	345	3,973 (2,585–5,360)	70.5 (59.4–81.6)
Institutional setting	7	~	~
While driving (incl. found in car)	0	~	~
Work, school, or place of recreation/sports	3	~	~
Outpatient setting	0	~	~
Other public property	6	~	~
Not documented	153	1,488 (861–2,115)	26.4 (15.2–37.6)

[†]Case counts and estimates from the National Electronic Injury Surveillance System - Cooperative Adverse Drug Event Surveillance (NEISS-CADES) project, CDC. “Mix-up errors” refers to accidental administration of the wrong insulin or mix-up of dosages when taking two or more insulin products.

[‡]All products reported in the ED medical record, including those implicated in the ED visit and those listed as concurrent medications. Insulin product types were assumed to be single agent formulations (e.g., “NovoLog”) unless specified as mix preparations (e.g., “NovoLog 70/30”). Ambiguous insulin mentions (e.g., “Humulin”, “Novolin”) were categorized as “Not documented”.

[§]Hypoglycemia identified by MedDRA-coded chart abstraction, based on documented clinician diagnosis and/or blood glucose value <70 mg/dL.

Abbreviations: ED, emergency department; CI, confidence interval; SGLT2, Sodium-glucose co-transporter-2; MedDRA, Medical Dictionary for Regulatory Activities

Table 4.

Factors Contributing to Insulin Mix-up Errors Among Voluntary Adverse Event Cases Reported to FAERS, 2016–2017[†]

Contributing Factors for Error	No. Cases	Illustrative Cases
Product Differentiation-Related Error		
Immediate container and/or labels look too similar within the same manufacturer's product line	6	69-year-old male on Novolin R (insulin human) and Novolin N (isophane insulin human suspension) vials at home. The patient administered the wrong insulin resulting in low and high blood glucose readings (50s to 400s mg/dL). The patient's wife reported difficulty distinguishing between the products due to similarities in the vial labels (including same color).
Immediate container and labels look too similar to another manufacturer's	4	57-year-old male on Humalog U-100 (insulin lispro) and Lantus (insulin glargine) pens at home. Patient administered 23 units of Humalog at bedtime thinking it was his Lantus pen. The resultant hypoglycemia was treated in the ER. The patient attributed his confusion to color similarity between the two pens.
Patient with visual impairment	4	Legally blind 77-year-old male on Humalog U-100 (insulin lispro) and Levemir (insulin detemir) pens at home. He accidently used his Humalog pen when he intended to administer the Levemir. The patient experienced symptoms of hypoglycemia overnight (52 mg/dL when checked), which he treated with food at home.
Comprehension-Related Error		
Confusion with device trade name	1	Female of unknown age on Basaglar (insulin glargine) via "KwikPen" and Apidra (insulin glulisine) pen at home. The patient was taking the Basaglar with each meal and the Apidra at bedtime. Per the report, the patient determined that the Basaglar was her mealtime insulin because of the device name "KwikPen". The patient experienced erratic control of her glucose due to the mix-up.
Patient confusion during transition of therapy	1	Male of unknown age on Lantus (insulin glargine), Novolog (insulin aspart), and Apidra (insulin glulisine) from vials. The patient confused either Novolog or Apidra with the vial of Lantus and experienced a severe hypoglycemic episode requiring treatment in the ER. The patient was discharged on Lantus and either Novolog or Apidra. The report is unclear which medication the patient was supposed to continue and stop (Novolog vs. Apidra).
Other accidental mix-up	6	62-year-old male on Novolog (insulin aspart) and Lantus (insulin glargine) pens at home. Patient administered his 15-unit dose of Novolog. He was reportedly rushed by family to complete administering his insulin doses, so he dialed his 45-unit insulin dose on the Novolog pen that he still held in his hand instead of reaching for his Lantus pen. The patient experienced hypoglycemia that he attempted to treat at home but eventually had to go to the ER for treatment.
Wrong drug prescribed	1	Male of unknown age on Novolog Mix 70/30 (insulin aspart protamine and insulin aspart suspension) at home. The patient's physician inadvertently prescribed Novolog (insulin aspart), which was dispensed by the pharmacy. After the patient took a dose, he experienced a low blood glucose of 14 mg/dL which required treatment in the ER. The reporter attributed the error to name similarity between the two products.
Wrong drug dispensed (proprietary name confusion: look-alike to another trade name)	2	79-year-old male on Humalog Mix 75/25 (insulin lispro protamine and insulin lispro suspension) pens at home. The caregiver administered the patient's normal dose using the pen dispensed from the pharmacy and the patient experienced hypoglycemia (reported a blood glucose 38 mg/dL), which was treated at home. The caregiver later confirmed with the pharmacy that the patient was erroneously dispensed a pen of Humalog (insulin lispro) along with his Humalog Mix 75/25 pens.
Wrong drug dispensed (other)	1	Female of unknown age using Humulin R U-100 (insulin human) via insulin pump at home. The patient's pharmacy dispensed Humulin R U-500 (insulin human) instead of Humulin R U-100 and she experienced severe hypoglycemia, which required hospitalization for treatment.
Dispensing of product sample by healthcare provider without a prescription	1	Female of unknown age on Humulin 70/30 (human insulin isophane suspension and human insulin) from a vial at home. After running out of medication, a nurse provided sample Humalog Mix 75/25 (insulin lispro protamine and insulin lispro suspension) pens. Outcome of error was not reported.
Not Provided	**31**	~
TOTAL	**58**	~

† Case descriptions are based on verbatim excerpts from FAERS reports with spelling corrected, abbreviations spelled out, and "blood sugar" replaced with "blood glucose". Brand names are reported verbatim as per case reports and generic names are provided in parentheses.

Abbreviations: FAERS, Food and Drug Administration Adverse Event Reporting System