Datamining Medication Error Reports in the FDA Adverse Event Reporting System (FAERS) to Supplement Strategies for Identifying Potential Safety Signals

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PLAIN LANGUAGE SYNOPSIS

Medication errors have a significant public health burden. Datamining, while used throughout FDA to detect adverse event safety signals, has not yet been fully evaluated for detecting medication error safety signals. This research demonstrates the efficacy of datamining for early detection of medication error safety signals.

BACKGROUND

A medication error, defined by the National Coordinating Council for Medication Error Reporting and Prevention, is "any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer."[1] Medication errors cost the American healthcare system approximately $21 billion per year according to the Network for Excellence in Health Innovation.[2] A 2020 meta-analysis found the pooled prevalence of preventable medication harm (medication errors resulting in adverse events) was 3%, of which 26% of those instances resulted in clinically severe or life-threatening preventable harm. [3]

The FDA's Division of Medication Error Prevention and Analysis (DMEPA) is responsible for monitoring and preventing medication errors related to the naming, labeling, packaging, and design for CDER-regulated drug products. [4] DMEPA's postmarket activities include surveilling medication error reports submitted by healthcare providers and consumers to the FDA Adverse Event Reporting System (FAERS). When a DMEPA safety reviewer identifies a medication error safety signal in FAERS, the reviewer logs the signal in an internal tracking database. The reviewer then evaluates the signal to determine if regulatory action is needed to mitigate the reported error.

Datamining refers to the use of complex data analytics to discover patterns of associations or unexpected occurrences ("signals") in large databases. [4] One type of datamining, disproportionality analysis, detects signals as increases in the relative rate of adverse events (including medication errors) in proportion to all other adverse events." [5] Several methods of disproportionality analyses have been studied for pharmacovigilance at the FDA including the Reporting Odds Ratio (ROR), the Proportional Reporting Ratio (PRR), Screened PRR (SPRR), and the method often used at FDA, Empiric Bayes Geometric Mean (EBGM). [4] [5] The EBGM is calculated using Multi-item Gamma-Poisson Shrinkage (MGPS). The FDA currently factors in the standard error of EBGM calculations by monitoring the lower bound of EBGM's 90% confidence interval, EB05. [6] The EB05 value decreases measurement sensitivity to reduce the number of false positives in signals generated by MGPS. An EB05 > 2 denotes 95% confidence that a drug-event is occurring more than twice the rate it was expected to occur. While these methods have been studied and used at FDA for detecting adverse event signals, the same methods have not been fully studied and validated for detecting medication error safety signals.

CITATIONS

[1] National Coordinating Council for Medication Error Reporting and Prevention, "About Medication Errors: What is a Medication Error?," [Online]. Available: https://www.nccmerp.org/about-medication-errors. [Accessed 2 October 2020].
[2] Network for Excellence in Health Innovation, "Preventing Medication Errors: A $21 Billion Opportunity," 2011. [Online]. Available: https://www.nehi.net/bendthecurve/sup/documents/Medication_Errors_%20Brief.pdf. [Accessed 21 September 2021].
[3] Hodkinson A, Tyler N, Ashcroft D, *et al*, "Preventable medication harm across health care settings: a systematic review and meta-analysis," 2020. BMC Medicine 18: 313.
[4] U.S. Food and Drug Administration, "Datamining," 21 August 2019. [Online]. Available: https://www.fda.gov/science-research/data-mining. [Accessed 26 April 2021]. See also: Data Mining at FDA -- White Paper
[5] DuMouchel W, Pregibon D, "Empirical Bayes screening for multi-item associations," in Proceedings of the seventh ACM SIGKDD international conference on Knowledge discovery and data mining, 2001.
[6] DuMouchel W, Pregibon D, "Evaluation of disproportionality safety signaling applied to healthcare databases," Drug Safety, pp. 36(Suppl 1):S1233-S132, 2013.

METHODS

Data Collection

Postmarket evaluations of medication error safety signals completed by DMEPA between 2019 and 2020 were analyzed in this study. Evaluations were excluded if they met at least one of the following criteria:

1. The evaluation was undertaken by DMEPA at the request of another FDA office.
2. The evaluation was not based on FAERS reports, or the evaluation was based on a single report, such as a provider who was unable to accurately scan a barcode (note that a single report may produce a variable signal from extremely high to undetectable EB05 values).
3. The investigator was unable to discern the initial log date for the signal.

Drug product names, medication error events, and dates DMEPA first logged the safety signals were collected from the written evaluations and from an internal tracking database.

Datamining

Empirica Signal's "Product Active Moiety (Suspect) by Quarter" run was used to calculate EB05 values for each safety signal dating back to at least 1 year before DMEPA logged the signal. Success in this study was primarily determined by a signal's associated drug-event pair having an EB05 value of 2 or greater and secondarily by the signal being identified by datamining before or during the quarter when DMEPA logged the signal.

RESULTS

Data Collection

Forty-six medication error signals evaluated by DMEPA between 2019 and 2020 were reviewed for this study. We excluded 23 evaluations for the following reasons: those undertaken by DMEPA at the request of another office (13), those that were not based on FAERS reports or were based on a single report (6), and those for which the investigator was unable to discern the initial log date for the signal (4). The remaining 23 signals were deemed appropriate for this study (Table 1, columns 1 and 2).

Datamining

Of the 23 signals included in this study, 70% (n = 16) were identified by Empirica Signal (Table 1, column 4). Additionally, 52% (n = 12) of the 23 signals were identified by Empirica Signal before or during the quarter when DMEPA logged the signal (Table 1, column 5). Four safety signals were not identifiable until after DMEPA logged the signal. The remaining 7 safety signals never met the detectable signal threshold of EB05 > 2.

Table 1. Datamining identified 70% (n = 16) of known medication error signals (column 4 in green) and identified 56% (n = 12) before or during the quarter that DMEPA logged the signal (column 5 in green).

Drug product active ingredient(s)	Description of medication error safety signal	Year.quarter that the error was first logged by DMEPA	Signaling medication error event(s) (MedDRA PT)	Year.quarter that the error was first identified by Empirica Signal
beclomethasone dipropionate	Not washing the inhaler potentially causing the device to not dispense drug	2019.2	Device malfunction	2015.4 or earlier
denosumab and pegfilgrastim	Potential mix-ups between denosumab and pegfilgrastim related to similar colors and dosage forms	2019.2	Intercepted product administration error	2016.3
erenumab	Potential mix-ups between cartons containing 1 autoinjector and others containing two autoinjectors	2019.3	Incorrect dose administered	2018.3
erenumab	Potential failure to leave product at room temperature 30 minutes prior to injection	2020.1	Wrong technique in product usage process; Wrong technique in device usage process	2018.3
estradiol	Potential confusion between products with once weekly dosing and others with twice weekly dosing	2019.1	Incorrect product administration duration	2016.1 or earlier
insulin aspart	Potential errors related to generic products not including strength on the label	2017.2	Wrong product administered; Product dispensing error; Intercepted product selection error	2016.1 or earlier
insulin human	Potential failure to prescribe or dispense U-500 syringes with insulin human U-500 vials	2018.1	Product dispensing error; Intercepted product dispensing error; Intercepted product administration error	2016.1 or earlier
ketorolac	Linear barcode potentially unscannable	2019.2	Product label issue	2017.1
lenvatinib	Potential errors related to labeling confusion associated with the 12 mg daily dose blister card packaging configuration	2019.4	Drug titration error	2019.1
semaglutide	Medication errors related to patients potentially unable to dial doses of medication on the device	2019.1	Product dispensing error	2018.2
ibuprofen and sevelamer	Potential mix-ups caused by tablet similarities	2018.4	Product appearance confusion	2018.4
remdesivir	Errors related to the wrong diluent being used to prepare the product or volume not being removed from the IV bag before mixing the product drawn from the vial	2020.2	Product preparation error; Product preparation issue	2020.2
enoxaparin	Needlestick injuries related to potential use errors	2018.4	Device malfunction	2020.4
naltrexone	Errors related to patients potentially self-administering the product	2018.4	Intercepted product administration error	2019.2
rasburicase	Errors related to diluent being potentially added to the infusion bag instead of the reconstituted drug	2018.4	Product preparation error	2019.1
rubidium-82	Potential elution with lactated ringers instead of sodium chloride that could cause unintended overexposure to radiation	2019.2	Product preparation issue	2019.4
filgrastim	Potential errors related to the wrong route of administration printed on the tray label	2020.3	not detected	not detected
methoxy polyethylene glycol-epoetin beta	Errors related to patients potentially receiving doses more frequently than recommended	2020.1	not detected	not detected
octreotide	Errors related to the labelling not indicating intravenous route of administration despite approval and prescribing information	2019.3	not detected	not detected
risperidone	Errors related to potential confusion associated with dose markings printed on the syringe plunger instead of the barrel	2019.2	not detected	not detected
sugammadex	Potential errors related to the product not being stored properly away from light	2018.1	not detected	not detected
tacrolimus	Potential confusion between the immediate-release and extended-release formulations	2019.3	not detected	not detected
temsirolimus	Potential errors related to product not being prepared by the intended two-step dilution process	2018.4	not detected	not detected

CONCLUSIONS

Empirica Signal successfully identified known medication error safety signals (70% of 23 known signals). This study suggests that datamining FAERS reports using EB05 values calculated using Empirica Signal's MGPS algorithm is a potential strategy to supplement DMEPA's current postmarket surveillance. Future studies will investigate the use of datamining to detect new or unknown medication error safety signals using Empirica Signal and improving upon these methods.

LIMITATIONS

In addition to known limitations of datamining FAERS, we encountered the following:

1. Underreporting of medication errors: the methods partially accounted for this limitation by identifying safety signals based on rates relative to the numbers of other events in the same database. Underreporting is a limitation that affects all forms of pharmacovigilance and is not unique to this study.
2. Empirica Signal limitations: to feasibly study historical datamining of medication errors, Empirica Signal's Product Active Moiety by Quarter (Suspect) run was utilized as it had the most historical data accessible, dating back to the fourth quarter of 2015. However, this meant that signals were only associated by active moiety, and not necessarily the specific products identified in each safety signal.
3. Event coding and narrative review: Medication errors are subject to inconsistent coding, in many cases caused by overlapping, ambiguous, and incomplete terminology. The investigator reviewed a small portion of the thousands of FAERS case reports included in this study, particularly the case narratives, to see if the errors were coded correctly. The drug events that generated these signals may not be exactly reflective of their respective medication error safety signals.
4. Lag time between identifying and logging the signal: there may have been lag time between when DMEPA identified a medication error safety signal and when the signal was logged into the internal database that was considered for this study.

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DISCLAIMER

The information in this presentation is not a formal dissemination of information by the FDA and does not represent Agency position or policy.

CONFLICTS OF INTEREST

No conflicts of interest to disclose.