Medication Error Pharmacovigilance and the FDA Sentinel System

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Medication Errors- Headline News

EMA to Review Methotrexate Overdose and Dosing

Psychiatric patient given wrong medication due to misspelling

CANADA October 26, 2016 5:54 am

Updated: October 26, 2016 9:13 pm

1 in 18 Canadian hospital patients

Your Health Care May Kill You:

News › Health

NHS medication errors contribute to as many as 22,000 deaths a year, major report shows

May 17, 2018 ▪ Volume 23 Issue 10

Acute Care ISMP Medication Safety Alert!®

Educating the Healthcare Community About Safe Medication Practices

QuarterWatch™ (Quarter 3 2017)

Emerging risks with inhaled medications using the Ellipta device, the controversy with antidepressants, and loperamide abuse

SAFETY briefs

Multivitamin injection label error. The vial label on the single dose INFUVITE Adult multiple vitamins injection, manufactured

Spanish medicines regulator, AEMPS

According to research by Désirée K… Medicine, in the 10-year period of 20… errors has almost quintupled.

Dutch hospitals pay out millions

Medication errors—an enduring problem for children and elderly patients

…: FDA cautions …ation error with …ceftazidime and

son to m…

PAMELA COWAN, REGINA LEADER-POST Updat…

Medical errors under the spotlight at key forum in Riyadh

Topics to Be Covered

1. How is a medication error defined?
2. What is the public health burden of medication errors?
3. Considerations for medication error pharmacovigilance.
4. How can large multisite electronic databases inform medication error analysis and prevention?

Medication Error Definition

- Literature review found 26 different definitions for medication error
  - Lisby M, et. al., How are medication errors defined? A systematic literature review of definitions and characteristics. Int J Qual Health Care 2010; 22(6):507-518.

- "A medication error 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"
  - National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP); available from: https://www.nccmerp.org/about-medication-errors [accessed 2 Aug 2018].

- Intentional or deliberate uses (e.g., abuse, misuse, off label use) are generally not considered medication errors

Public Health Burden of Medication Errors

- "A total of 0.7% of global total health expenditure (THE) or **42 [billion] USD** worldwide, can be avoided if medication errors are prevented."
  - Aitken M, et. al., Advancing the responsible use of medicines: applying levers for change. IMS Institute for Healthcare Informatics, 2012.

- "Estimated that **237,396,371** medication errors occur at some point in the medication use process in England per annum."
  - Elliot RA, et. al., Prevalence and economic burden of medication errors in the NHS in England. Manchester Centre for Health Economics, 2018.

- Among adult outpatients…**52% (95% CI: 42–62%) of adverse drug reactions were preventable**. Among inpatients…45% (95% CI: 33–58%) of adverse drug reactions were preventable [errors].
  - Hakkarainen KM, et. al., Percentage of patients with preventable adverse drug reactions and preventability of adverse drug reactions – a meta-analysis. PLoS One. 2012.

Medication Without Harm: WHO's Third Global Patient Safety Challenge

World Health Organization | About us | Health topics | News | Countries

WHO launches global effort to halve medication-related errors in 5 years

29 March 2017 | News Release | GENEVA/BONN

WHO today launched a global initiative to reduce severe, avoidable medication-associated harm in all countries by 50% over the next 5 years.

The Global Patient Safety Challenge on Medication Safety aims to address the weaknesses in health systems that lead to medication errors and the severe harm that results. It lays out ways to improve the way medicines are prescribed, distributed and consumed, and increase awareness among patients about the risks associated with the improper use of medication.

Medication errors cause at least one death every day and injure approximately 1.3 million people annually in the United States of America alone. While low- and middle-income countries are estimated to have similar rates of medication-related adverse events to high-income countries, the impact is about twice as much in terms of the number of years of healthy life lost. Many countries lack good data, which will be gathered as part of the initiative.

Globally, the cost associated with medication errors has been estimated at US$ 42 billion annually or almost 1% of total global health expenditure.

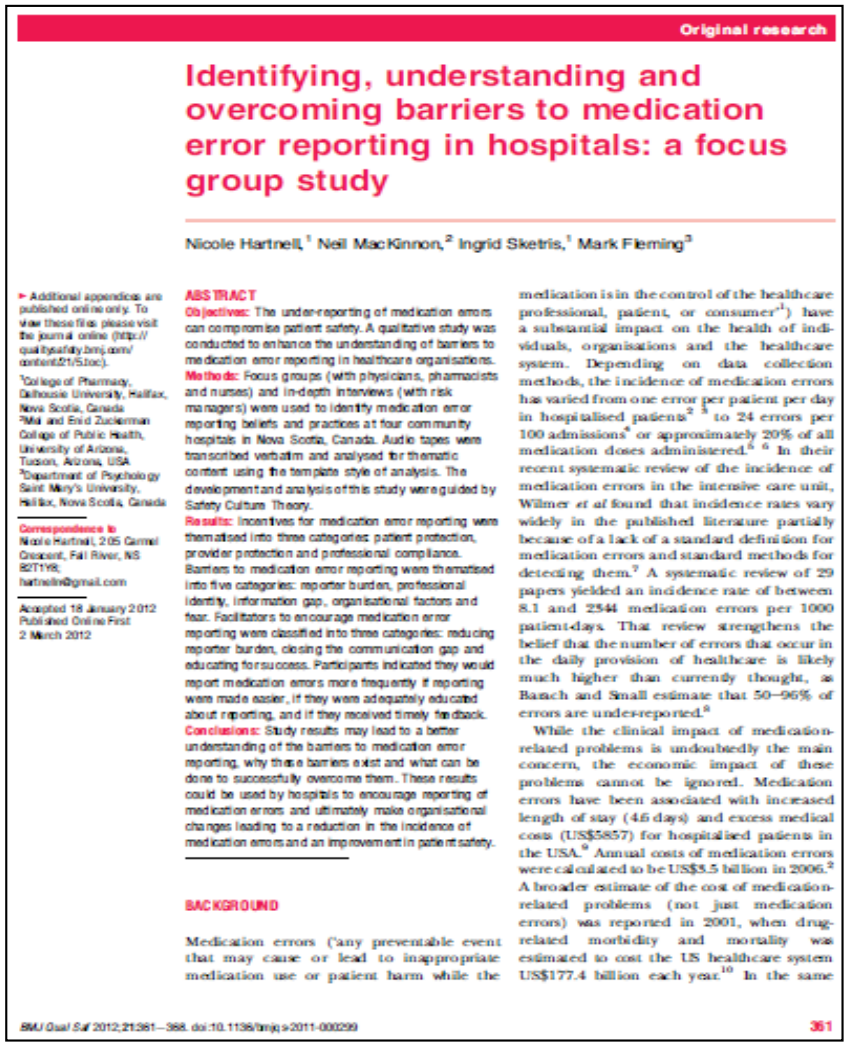
"We all expect to be helped, not harmed, when we take medication," said Dr Margaret Chan, WHO Director-General. "Apart from the human cost, medication errors place an enormous and unnecessary strain on health budgets. Preventing errors saves money and saves lives."

Every person around the world will at some point in their life take medicines to prevent or treat illness. However, medicines do sometimes cause serious harm if taken incorrectly, monitored insufficiently or as the result of an error, accident or communication problems.

Both health workers and patients can make mistakes that result in severe harm, such as ordering, prescribing, dispensing, preparing, administering or consuming the wrong medication or the wrong dose at the wrong time. But

CONSIDERATIONS FOR MEDICATION ERROR PHARMACOVIGILANCE

Underreporting of Medication Errors



Original research

Identifying, understanding and overcoming barriers to medication error reporting in hospitals: a focus group study

Nicole Hartnell,[1] Neil MacKinnon,[2] Ingrid Sketris,[1] Mark Fleming[3]

► Additional appendices are published online only. To view these files please visit the journal online (http://qualitysafety.bmj.com/content/21/5/toc).

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Accepted 18 January 2012
Published Online First 2 March 2012

ABSTRACT

Objectives: The under-reporting of medication errors can compromise patient safety. A qualitative study was conducted to enhance the understanding of barriers to medication error reporting in healthcare organisations.

Methods: Focus groups (with physicians, pharmacists and nurses) and in-depth interviews (with risk managers) were used to identify medication error reporting beliefs and practices at four community hospitals in Nova Scotia, Canada. Audio tapes were transcribed verbatim and analysed for thematic content using the template style of analysis. The development and analysis of this study were guided by Safety Culture Theory.

Results: Incentives for medication error reporting were thematised into three categories: patient protection, provider protection and professional compliance. Barriers to medication error reporting were thematised into five categories: reporter burden, professional identity, information gap, organisational factors and fear. Facilitators to encourage medication error reporting were classified into three categories: reducing reporter burden, closing the communication gap and educating for success. Participants indicated they would report medication errors more frequently if reporting were made easier, if they were adequately educated about reporting, and if they received timely feedback.

Conclusions: Study results may lead to a better understanding of the barriers to medication error reporting, why these barriers exist and what can be done to successfully overcome them. These results could be used by hospitals to encourage reporting of medication errors and ultimately make organisational changes leading to a reduction in the incidence of medication errors and an improvement in patient safety.

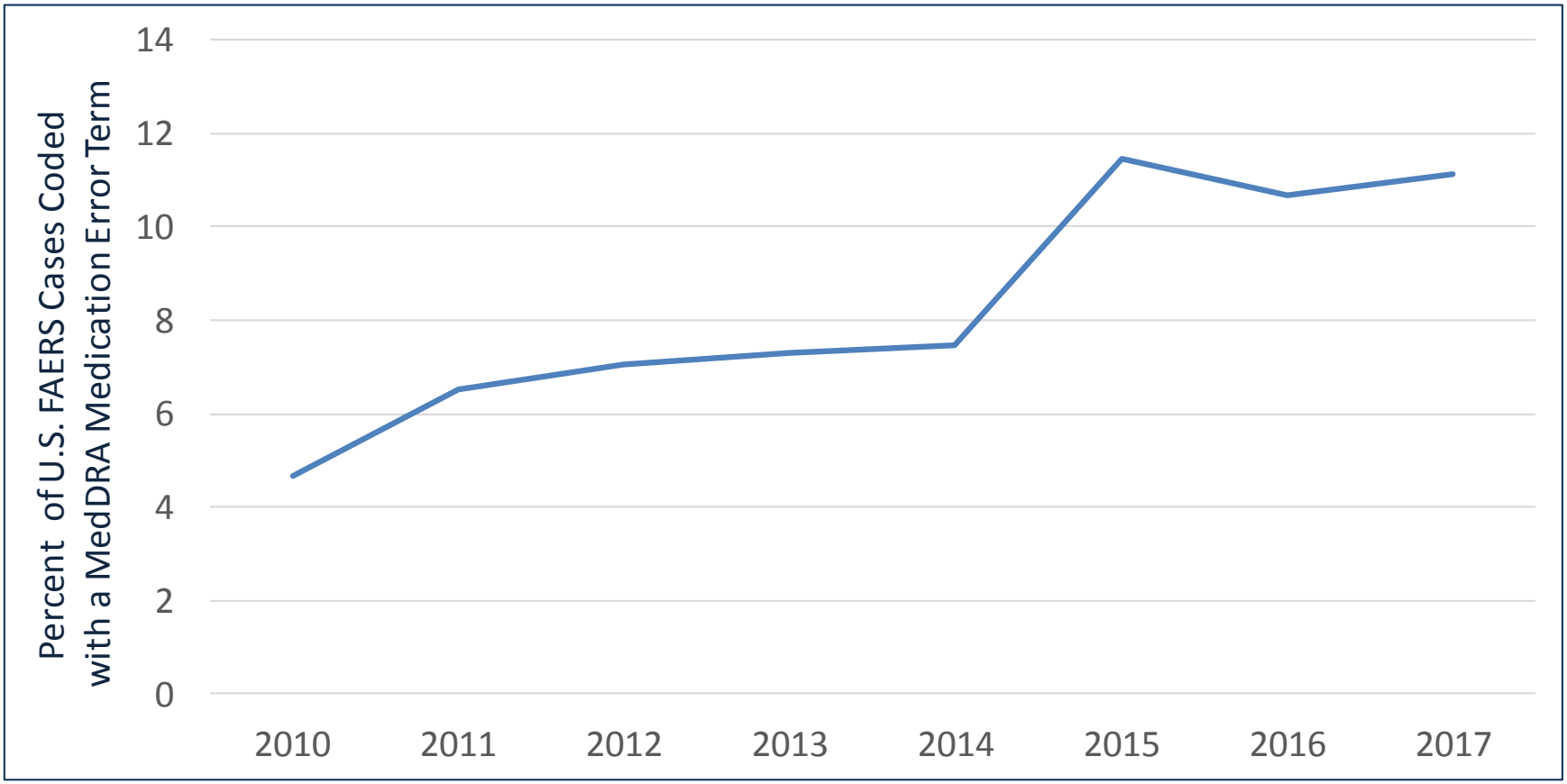
BACKGROUND

Medication errors ('any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the healthcare professional, patient, or consumer'[1]) have a substantial impact on the health of individuals, organisations and the healthcare system. Depending on data collection methods, the incidence of medication errors has varied from one error per patient per day in hospitalised patients[2 3] to 24 errors per 100 admissions[4] or approximately 20% of all medication doses administered.[5 6] In their recent systematic review of the incidence of medication errors in the intensive care unit, Wilmer *et al* found that incidence rates vary widely in the published literature partially because of a lack of a standard definition for medication errors and standard methods for detecting them.[7] A systematic review of 29 papers yielded an incidence rate of between 8.1 and 2544 medication errors per 1000 patient-days. That review strengthens the belief that the number of errors that occur in the daily provision of healthcare is likely much higher than currently thought, as Barach and Small estimate that 50–96% of errors are under-reported.[8]

While the clinical impact of medication-related problems is undoubtedly the main concern, the economic impact of these problems cannot be ignored. Medication errors have been associated with increased length of stay (4.6 days) and excess medical costs (US$5857) for hospitalised patients in the USA.[9] Annual costs of medication errors were calculated to be US$5.5 billion in 2006.[3] A broader estimate of the cost of medication-related problems (not just medication errors) was reported in 2001, when drug-related morbidity and mortality was estimated to cost the US healthcare system US$177.4 billion each year.[10] In the same

- Regulatory reporting requirements
- Fear of punishment or litigation
- Embarrassment of having been involved a medication error
- Lack of reporting forms tailored for medication errors
- Workload; not knowing where, why, or what to report

% of U.S. Cases in the FDA Adverse Event Reporting System (FAERS) Coded with a Medication Error Term*



*Based on the MedDRA SMQ *Medication errors (narrow)*, V21

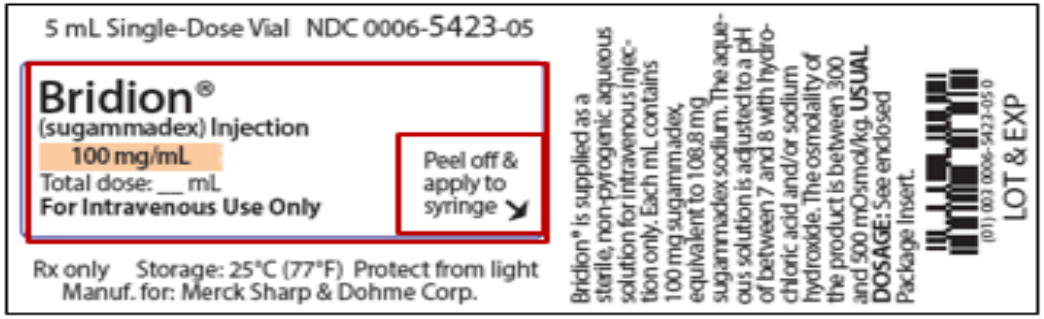
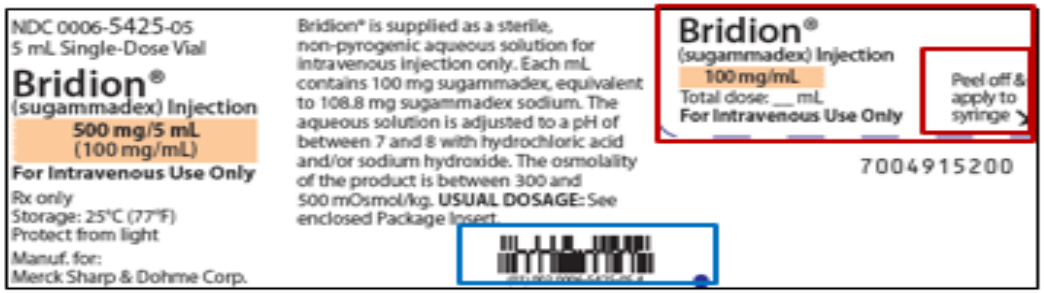
Incomplete FAERS Reports

- Reports often lack information necessary to inform appropriate regulatory action:
  - What was the cause and contributing factors for the error?
  - Where did the error originate?
  - What does the reporter recommend to mitigate the error?
  - What population is at risk?
- U.S. Medwatch and E2B reporting forms are designed to primarily capture adverse event information, not medication errors
- *Risk: Revisions to labeling, packaging, drug names, or product design can introduce new types of errors*

Effectiveness of Regulatory Recommendations to Prevent Errors

- Effectiveness of regulatory actions often determined by postmarket spontaneous reports submitted to FAERS
- As part of the drug product approval process, FDA performs premarket reviews of proposed labeling, packaging, drug names, and product design to minimize errors
- FDA monitors postmarket medication error reports to identify safety signals
- Safety signals may result in labeling revisions or other regulatory actions, and also inform FDA's overall premarket review process

Case Example-Container Label

• Initial label • Wrong dose error reported • Cause: confusion with the total amount in the vial	
• Revised label • Peel-off label and barcode relocated • Potential wrong drug errors reported • Cause: scanners unable to read horizontal barcode	
• Revised label (current label) • Barcode relocated to vertical position	

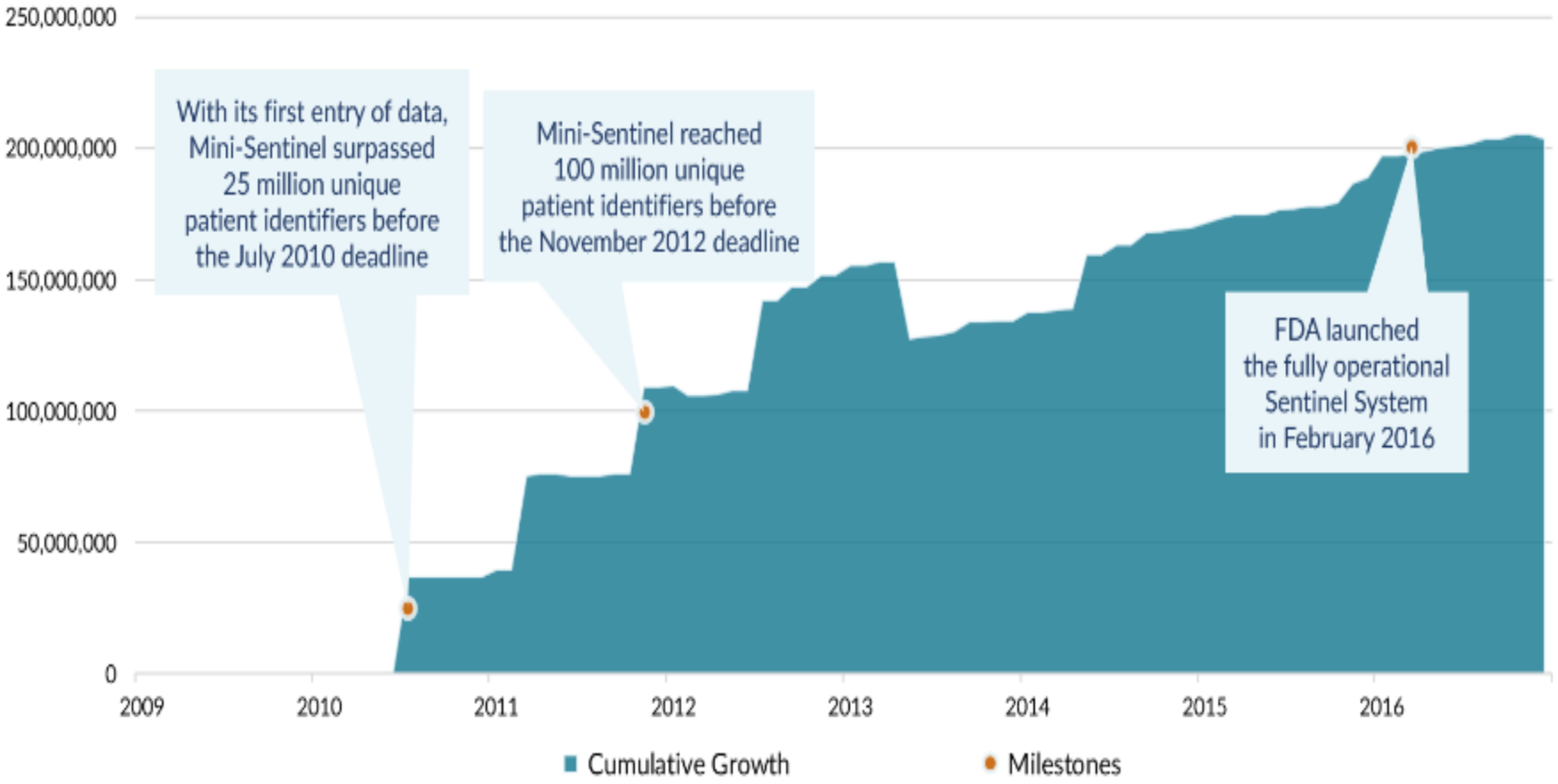
Source: Institute for Safe Medication Practices. ISMP Med Saf Alert Acute Care. 2018; 23(15).

USE OF FDA'S SENTINEL SYSTEM FOR MEDICATION ERROR ANALYSIS AND PREVENTION

FDA Sentinel System

- Sentinel is a large multisite electronic database comprised of 18 data partners
- Data partners maintain physical control of their data, and analytic programs are delivered and executed behind each data partner's firewall to protect privacy
- Sentinel has access to laboratory, pharmacy and medical records
- Sentinel contains 292 million cumulative unique patient identifiers between 2000 and 2017

Growth of the Sentinel Distributed Database



The area above depicts the cumulative number of unique patient identifiers in the Sentinel Distributed Database from 2010 to present. If patients move health plans, they may have more than one patient identifier.

Use of Sentinel for Medication Error Analysis and Prevention

- Sentinel provides real-world evidence from a large population dataset
- Depending on the type of medication error:
  - May address limitations of medication error underreporting and incomplete reports seen with spontaneous postmarket reports submitted to FAERS
  - Potentially able to assess trends for the impact of labeling revisions and other regulatory actions
  - Potentially useful to determine incidence, patient populations at risk, outcomes, stage (e.g., prescribing, dispensing, administration) in the medication use system where an error originated, and causes or contributing factors for the error (may require chart review)
- Currently being used for follow up investigations of signals and descriptive analysis

Case Example-Methotrexate

- Request from the Institute for Safe Medication Practices “to prevent methotrexate wrong frequency errors”
- Taking methotrexate daily instead of the intended weekly administration for rheumatoid arthritis can result in serious adverse events leading to death
- Methotrexate was FDA-approved in 1953; widely used
- FAERS contained 12 U.S. methotrexate wrong frequency reports between 2010 and 2017, including 2 deaths; most of the reports were incomplete
- We consulted the Sentinel System to characterize the incidence, cause, outcomes, and stage (e.g., dispensing, prescribing) where the error was occurring so we could target appropriate regulatory action

Conclusion

- Medication errors are a global public health burden
- Recent advances in large multisite electronic databases such as Sentinel have created opportunities to better characterize and mitigate the risks of medication errors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Methotrexate Wrong Frequency Error:
Detection and Confirmation of Daily Instead of Weekly Dosing

Kaiser Permanente Harvard Pilgrim Healthcare Inst U.S. FDA

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  - Michael Nguyen

Disclosure

- Funding source: U.S. Food and Drug Administration
- Potentially conflicting relationships: No relationships to disclose.

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Methotrexate

- Abbreviation: MTX
- Recommended dose for rheumatoid arthritis is 7.5 to 25 mg per week.
- Dispensed in 2.5 mg pills.
- Side effects are common.

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Methotrexate prescription label

- 7.5 mg (three tablets) to be taken WEEKLY on Monday.
- Take as directed.
- Take 2.5 mg (1 pill) of methotrexate on Monday and folate on Tuesday of the first week. Then increase to 5 mg (2 pills) of methotrexate on Monday and folate on Tuesday of the second week.

Wrong Frequency Error

- MTX is taken daily instead of weekly
- Prescribing
  - Physician writes “daily” instead of “weekly”
- Dispensing
  - Pharmacist fills incorrectly
- Administering
  - Patient misunderstands instructions
  - Patient mixes up her pills
  - Caregiver doesn’t understand the regimen

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Side effects and adverse effects

- Mouth sores, mucositis
  - Mild mucositis is a common side effect
  - Severe mucositis and inability to eat lead to cessation of therapy and hospitalization
- Acute renal failure
- Myelosuppression

Objective

- Long-term
  - Estimate the incidence of MTX wrong frequency errors in the United States through use of the FDA's Sentinel System.
- Immediate
  - Prototype: Develop and confirm an algorithm that can be implemented in the Sentinel System.
  - Estimate the incidence rate of frequency error at our setting.

Kaiser Permanente Northern California

- 4 million members
- Capitated, comprehensive care
- Electronic medical record
- Dropdown menus to write prescription orders
- Large, established research department

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Study cohort

- Eligibility criteria:
  - Rheumatoid arthritis with or without psoriasis
  - ≥1 dispensing of oral MTX during 2010-15
  - Excluded cancer patients
  - New MTX users: no earlier dispensing in the preceding year
  - Prevalent MTX users: ≥1 dispensing in the preceding year
- Data used to identify the cohort:
  - KPNC electronic medical record data formatted into Sentinel Common Data Model

Identifying potential wrong frequency errors using Sentinel Common Data Model

1. Number of pills divided by the days to next dispensing

   56 mg/week = 2.5 mg/pill * (96 pills / 30 days) * 7 days/week

2. Emergency department or inpatient diagnostic code for serious adverse drug event (ICD-9 995.20)

   995.20 Unspecified adverse effect of unspecified drug, medicinal and biological

Identifying potential wrong frequency errors using Kaiser Permanente EMR

- Rescue therapy using injected leucovorin (in/out patient)
  - Identifiable in KPNC using text search of medication orders.
    - Not feasible in Sentinel CDM.
  - Identifiable in Sentinel CDM using specific HCPCS code J0640 (leucovorin injection)
    - Identified 1 of 5 KPNC potential cases, 1 or 3 true cases.

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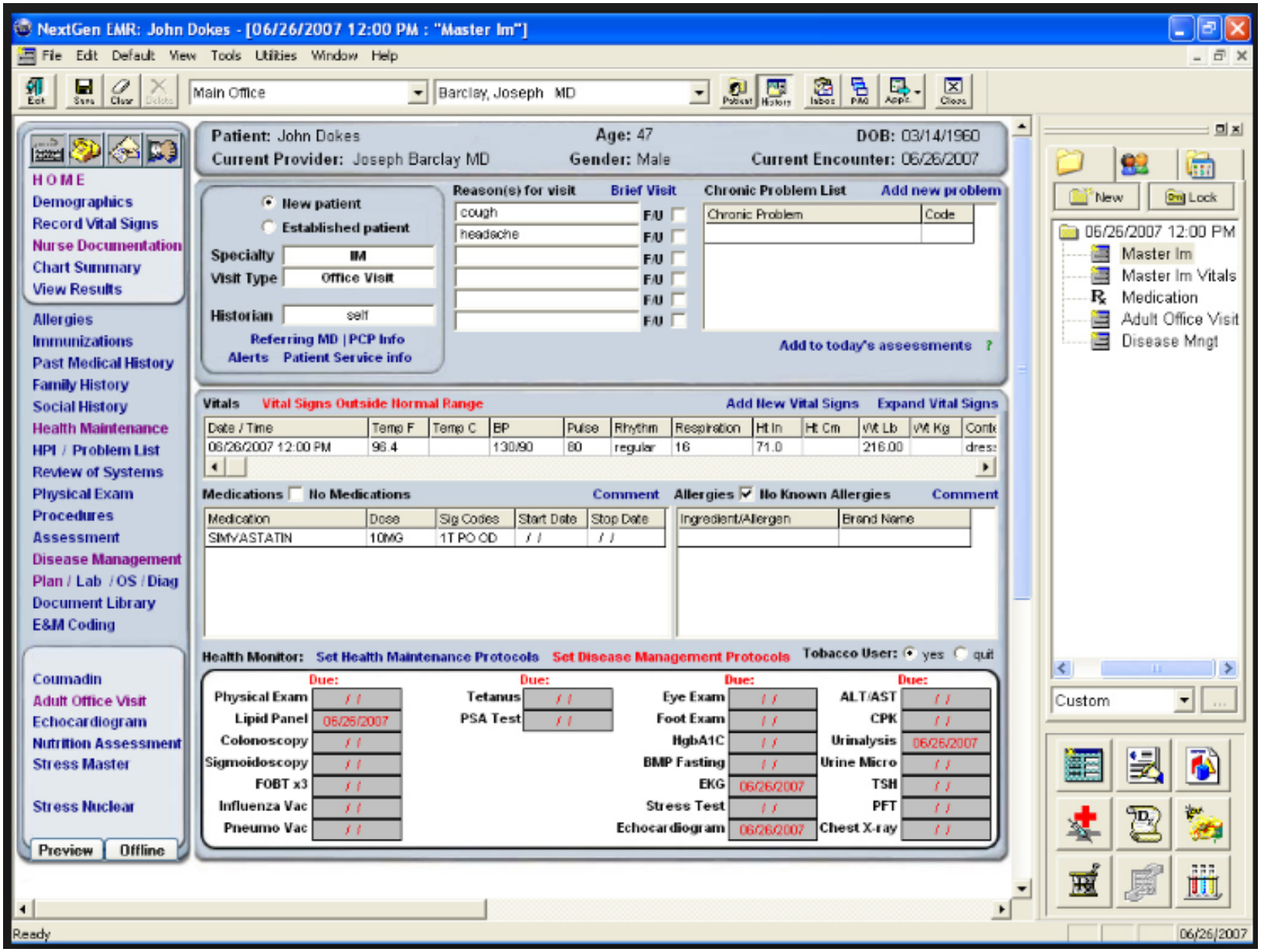
Confirmation of potential wrong frequency errors

- Chart review
  - Reviewed prescription label written by the prescriber
  - Read prescriber's notes to understand the patient's circumstances
  - Read all notes of utilization recorded into the EMR to gain insight



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Potential and Confirmed Frequency Errors

New MTX user, N=722	Existing MTX user, N=23,807
Flagged with potential frequency error, N=46	Flagged with potential frequency error, N=607
Chart review, N=46	Chart review, N=48
Confirmed with frequency error, N=3	Confirmed with frequency error, N=0

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Confirmation of potential wrong frequency errors using chart review

- Number of pills, days to next dispensing

  56 mg/week = 2.5 mg/pill * (96 pills / 30 days) * 7 days/week

  - 0 of 34 confirmed
- Emergency department or inpatient diagnostic code for serious adverse drug event (ICD-9 995.20)

  995.20 Unspecified adverse effect of unspecified drug, medicinal and biological

  - 0 of 4 confirmed
- Rescue therapy using leucovorin
  - 3 of 5 confirmed (PPV, 60%)

Underlying reasons for frequency errors

Advanced age
(2 patients)

Limited English
(1 patient)

Incidence rate of frequency error in our setting

- New MTX users, 3 confirmed among 722 users = 0.4%

- Existing MTX users, 0 confirmed among 23,807 users.

Learnings

- Needle in a haystack
  - Content experts were very helpful.
  - Exploratory data analysis was essential.
- All frequency errors occurred among new MTX users.
- The Days Supply variable was wrong only 1.5% of the time, but the adverse event rate was even lower.
- Rescue therapy with injected leucovorin was specific to overdose.
- Low-dose oral leucovorin was used to manage side effects.
- Future research could assess
  - E980.5 (poisonings by unspec drug or medicine)
  - 963.1 (poisoning by antineoplastic/immunosuppressive drug)

Thank you

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Medication Errors: Confused Drug Names

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1. Harvard Pilgrim Health Care Institute

2. HealthCore

3. U.S. Food and Drug Administration

August 24th 2018

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- This presentation reflects the views of the authors and not necessarily those of the U.S. FDA

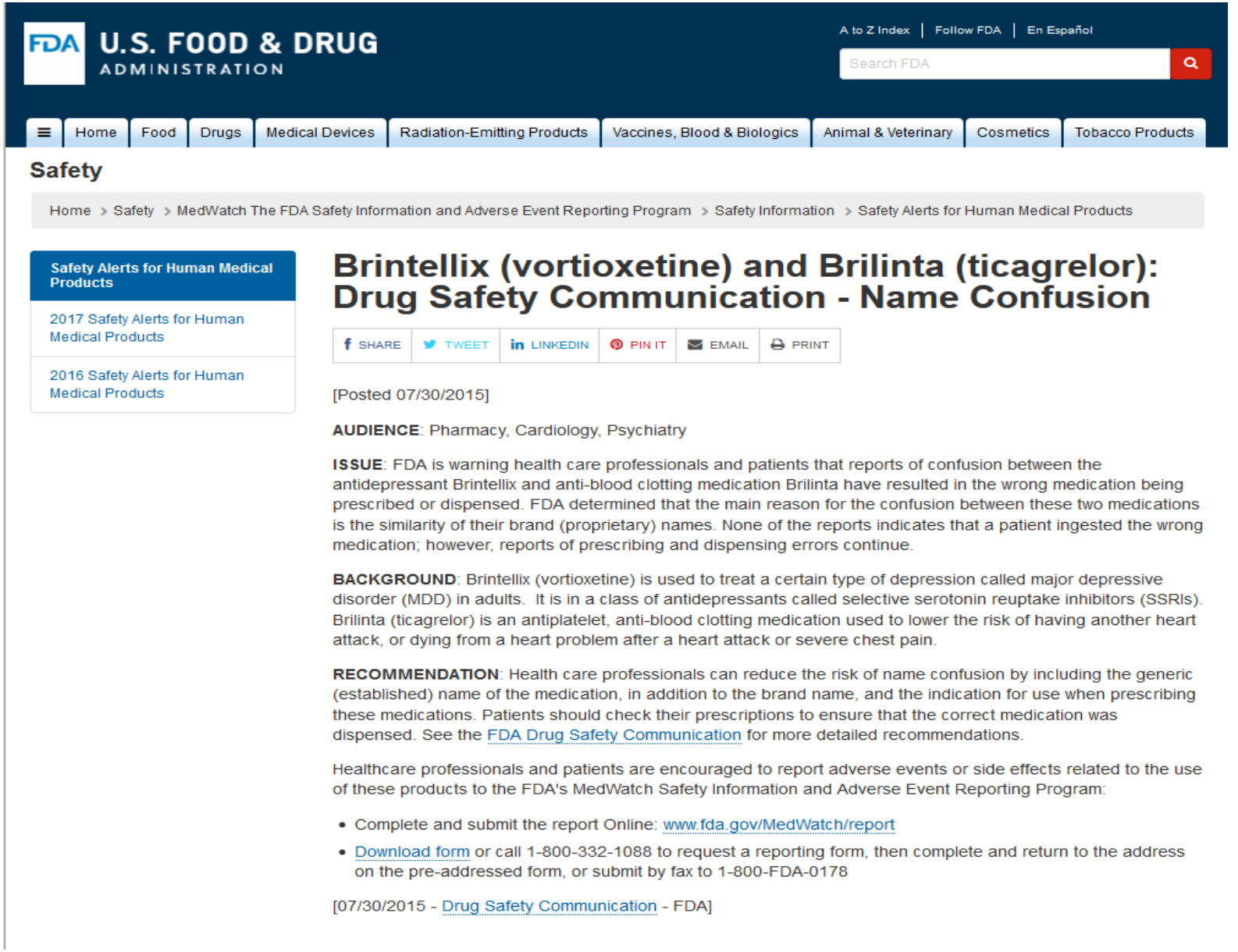
About Sentinel

- The U.S. Food and Drug Administration's (FDA) Sentinel Initiative is a long term effort to improve the FDA’s ability to identify and assess medical product safety issues.
- The Sentinel System is an active surveillance system that uses routine querying tools and pre-existing electronic healthcare data from multiple sources to monitor the safety of regulated medical products.

Background: Confused Drug Names

- Healthcare providers rely on a product's name as a critical identifier when prescribing, dispensing, and administering a drug product.
- Product names that look or sound-alike can cause or contribute to patients receiving the wrong drug product.
- As part of the preapproval process for new drug products, FDA reviews, and determines the acceptability of proposed proprietary names to minimize medication errors associated with product name confusion. FDA will revise proprietary names post-approval to prevent name confusion if warranted.
- July 2015: FDA drug safety communication[1] regarding medication errors in prescribing or dispensing due to brand name confusion with the antidepressant **Brintellix** (vortioxetine) and the antiplatelet **Brilinta** (ticagrelor)

[1] July 2015: https://www.fda.gov/Drugs/DrugSafety/ucm456341.htm



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Safety Alerts for Human Medical Products

2017 Safety Alerts for Human Medical Products

2016 Safety Alerts for Human Medical Products

Brintellix (vortioxetine) and Brilinta (ticagrelor): Drug Safety Communication - Name Confusion

SHARE TWEET LINKEDIN PIN IT EMAIL PRINT

[Posted 07/30/2015]

AUDIENCE: Pharmacy, Cardiology, Psychiatry

ISSUE: FDA is warning health care professionals and patients that reports of confusion between the antidepressant Brintellix and anti-blood clotting medication Brilinta have resulted in the wrong medication being prescribed or dispensed. FDA determined that the main reason for the confusion between these two medications is the similarity of their brand (proprietary) names. None of the reports indicates that a patient ingested the wrong medication; however, reports of prescribing and dispensing errors continue.

BACKGROUND: Brintellix (vortioxetine) is used to treat a certain type of depression called major depressive disorder (MDD) in adults. It is in a class of antidepressants called selective serotonin reuptake inhibitors (SSRIs). Brilinta (ticagrelor) is an antiplatelet, anti-blood clotting medication used to lower the risk of having another heart attack, or dying from a heart problem after a heart attack or severe chest pain.

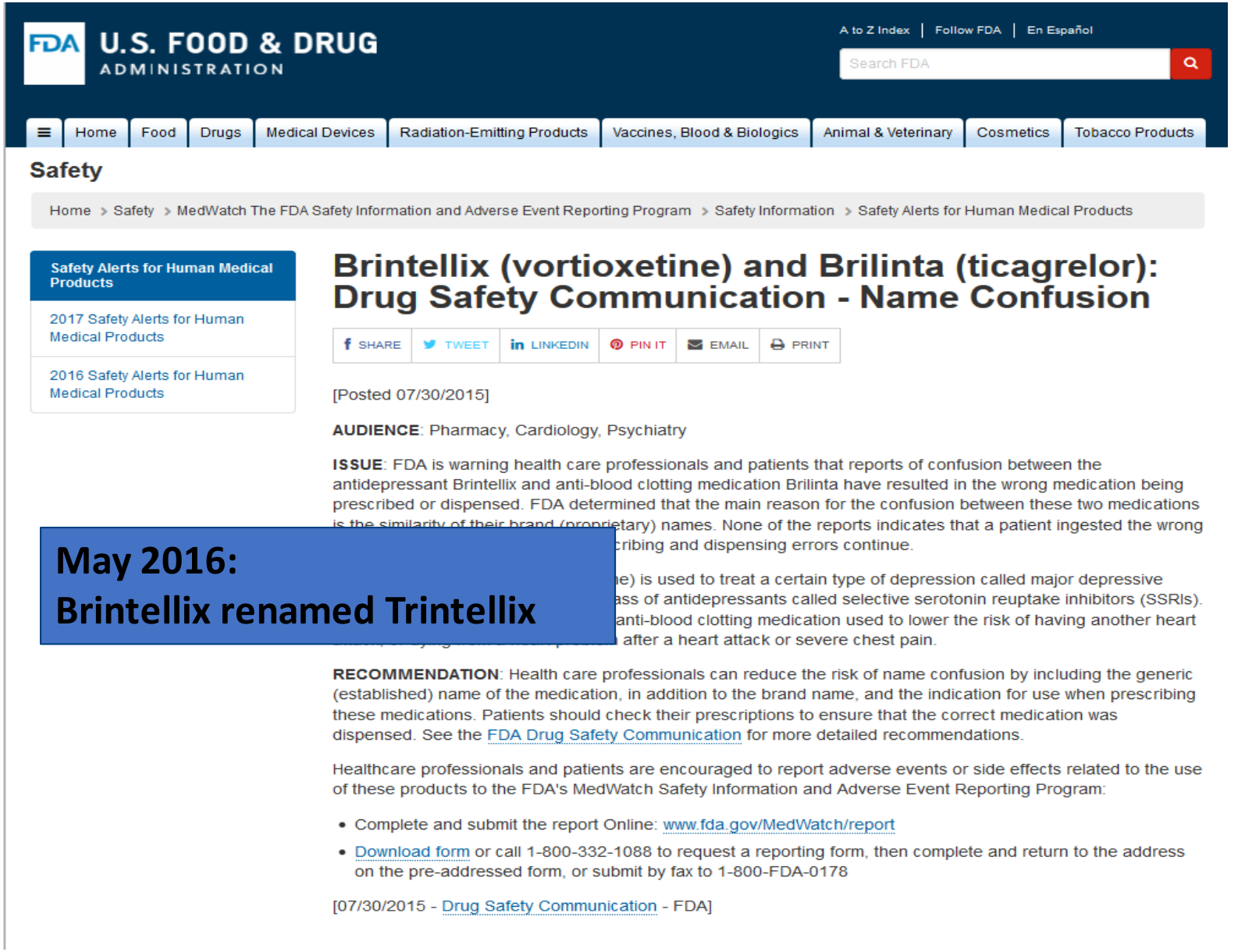
RECOMMENDATION: Health care professionals can reduce the risk of name confusion by including the generic (established) name of the medication, in addition to the brand name, and the indication for use when prescribing these medications. Patients should check their prescriptions to ensure that the correct medication was dispensed. See the FDA Drug Safety Communication for more detailed recommendations.

Healthcare professionals and patients are encouraged to report adverse events or side effects related to the use of these products to the FDA's MedWatch Safety Information and Adverse Event Reporting Program:

- Complete and submit the report Online: www.fda.gov/MedWatch/report
- Download form or call 1-800-332-1088 to request a reporting form, then complete and return to the address on the pre-addressed form, or submit by fax to 1-800-FDA-0178

[07/30/2015 - Drug Safety Communication - FDA]

https://www.fda.gov/Drugs/DrugSafety/ucm497942.htm



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[07/30/2015 - Drug Safety Communication - FDA]

May 2016:
Brintellix renamed Trintellix

https://www.fda.gov/Drugs/DrugSafety/ucm497942.htm

Objective

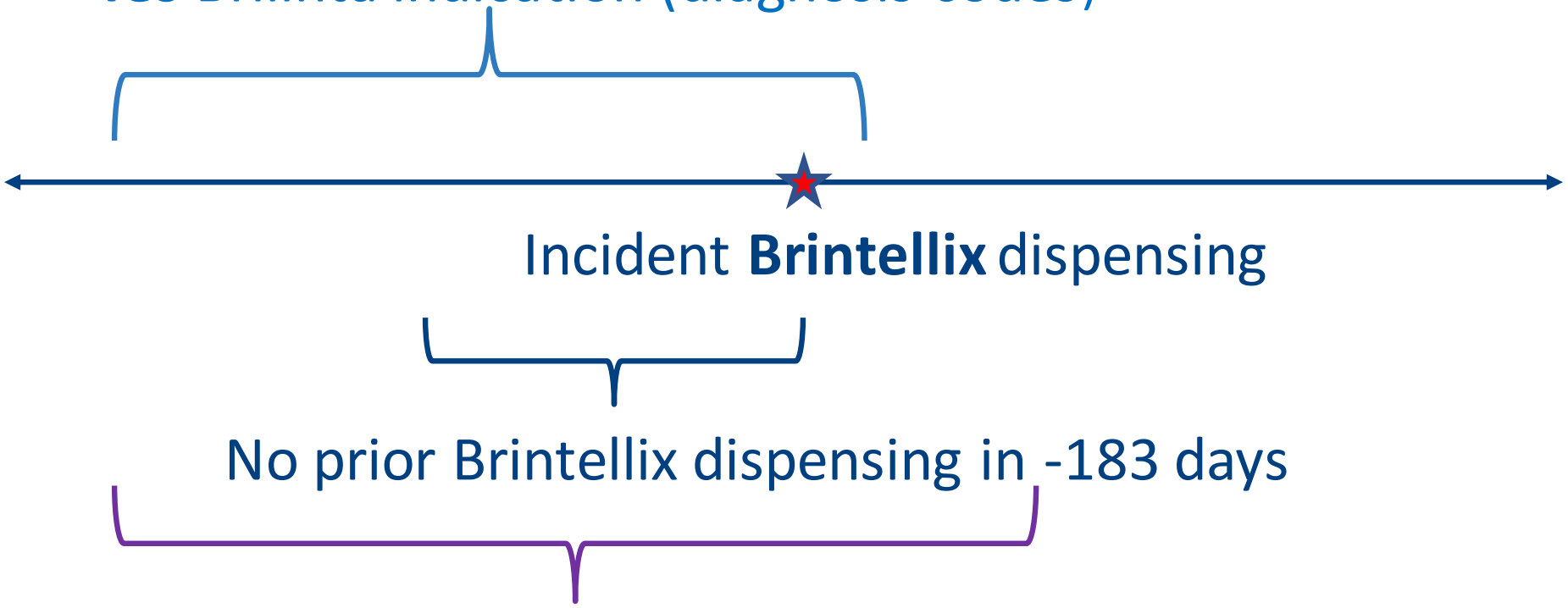
- To assess whether name confusion medication errors could be identified in the U.S. FDA's Sentinel System by assessing the presence and absence of on- and off-label indications in claims data

Methods

- Identified new users of Brintellix, and separately of Brilinta, 183 day washout; 9/30/2013 – 9/30/2015
- Members from 16 health plans enrolled with medical and pharmacy coverage for ≥365 days prior to dispensing date
- Post-exposure enrollment of 30 days

Assess on- and off-label indications in -365 through +30 days

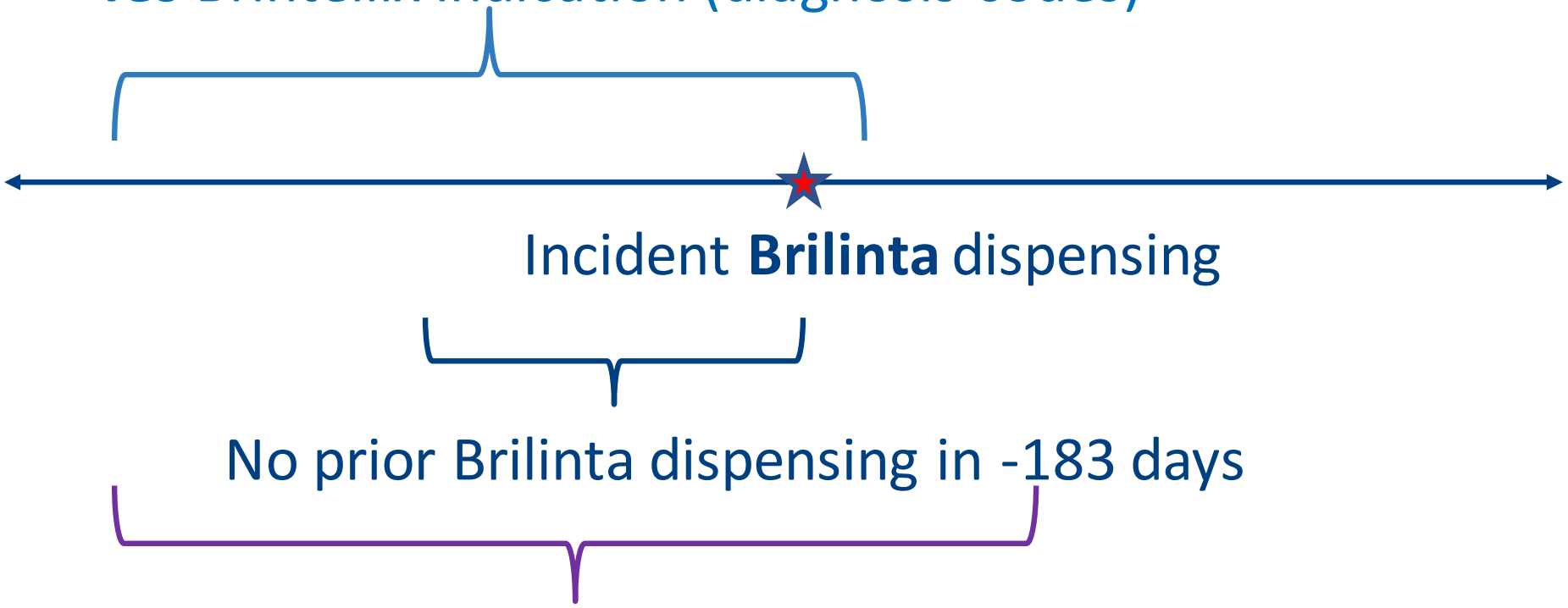
- **No** Brintellix indication (diagnosis codes)
- **Yes** Brilinta indication (diagnosis codes)



Assess on- and off-label indications in Patient Episode Profile Review (PEPR) **claims profile review** -365 days through +90 days

Assess on- and off-label indications in -365 through +30 days

- **No** Brilinta indication (diagnosis codes)
- **Yes** Brintellix indication (diagnosis codes)



Assess on- and off-label indications in PEPR **claims profile review**
-365 days through +90 days

Methods

Brintellix

- Indication:
  - Depression
- Off-label indications:
  - Schizophrenia
  - Episodic mood disorders
  - Anxiety disorders
  - Personality disorders
  - Bipolar depression
  - Post Traumatic Stress Disorder (PTSD)
  - Chronic pain

Brilinta

- Indications:
  - Acute coronary syndrome
  - Myocardial infarction
- Off-label indications:
  - Peripheral arterial disease
  - Unstable angina
  - Stroke
  - Stent

Patient Episode Profile Review (PEPR)

- An individual patient claims profile with code look ups merged to build a readable profile
- A way to retrieve a patient level dataset that provides a “claims line list” for some period surrounding an index date
  - Dataset can remain at the Data Partner
- Ability to further investigate an “alert” from aggregate data
  - “Poor Man’s Chart Review” with a case definition– Was the outcome associated with exposure or are there alternative explanations?
  - Can save time and resources with respect to medical chart retrieval

Data Partner Clinical Review of PEPR claims line list

- Goal: Review patient claims profile for potential appropriate, potential error, or inconclusive
- Find the index day and determine what was dispensed. What else was dispensed that day? Lots of cardiac drugs?
- Look back over the whole profile to get a sense of what types of drugs have been dispensed? Was the index drug dispensed prior? What about drugs in the classes of interest?
- Review the month prior. Any recent cardiac hospitalizations?
- Review pre-index date for diagnoses of interest
- Review post-index for refills of index medication
- Review post-index for diagnoses of interest

Example PEPR - A “Claims Line List"

day	EncType	CodeCat	CodeType	ClinCode	First	RxAmt	RxSup	CodeShortDescr
-18	AV	DX	9	7212				THORACIC SPONDYLOSIS
-18	AV	DX	9	72283				POSTLAMINECTOMY SYND LUMBAR
-18	AV	DX	9	7244				LUMBOSACRAL NEURITIS UNSPEC
-18	AV	PX	C4	99213				OFFICE/OUTPATIENT VISIT EST
-18	RX	RX	11	50458082004	F	90	30	Tapentadol HCl Tab 50 MG
-10	RX	RX	11	591530710	F	12	3	Promethazine HCl Tab 25 MG
-5	RX	RX	11	55111046805		14	14	Metoprolol Succinate Tab ER 24HR 100 MG
0	RX	RX	11	186077760	F	60	30	Ticagrelor Tab 90 MG
12	RX	RX	11	50458082004		90	30	Tapentadol HCl Tab 50 MG
16	RX	RX	11	93738698		60	30	Venlafaxine HCl Cap ER 24HR 150 MG
16	RX	RX	11	60505006502		30	30	Omeprazole Cap Delayed Release 20 MG
26	AV	DX	9	29622				MAJOR DEPRESSIVE DIS MOD
26	AV	PX	C4	99214				OFFICE/OUTPATIENT VISIT EST
38	RX	RX	11	186077760		60	30	Ticagrelor Tab 90 MG

PEPR Profile Review

- PEPR is a tool to help refine Cohort Identification and Descriptive Analysis (CIDA) requirements and evaluate potential medication errors
- Need chart review to be conclusive

	CIDA	After PEPR review		
Brilinta	potential Brilinta error	likely error	inconclusive	not an error
Total	51	4	6	41
Brintellix	potential Brintellix error	likely error	inconclusive	not an error
Total	27	16	6	5

https://www.sentinelinitiative.org/sentinel/surveillance-tools/routine-querying-tools/routine-querying-system

Discussion

- Sentinel query tools can be used to identify and describe potential medication errors in administrative data
- Tools exist to review claims profiles to refine query specifications
- Profile reviews offer an opportunity to potentially assess medication error
  - Chart review is needed to be conclusive
- Further application of the tools to asses medication errors will further refine available tools
- Limitation: multiple reviewers

Acknowledgements

- Many thanks are due to Data Partners who provided data used in the analysis
- Special thanks to the Data Partner reviewers

Look-a-Like

Sound-a-Like

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Medication errors
European perspective and analyses

34th International Conference on Pharmacoepidemiology & Therapeutic Risk Management

Presented by:
Rodrigo Postigo - Pharmacovigilance and Epidemiology Department
European Medicines Agency

European Union – Pharmacovigilance legislation

The European Union (EU) pharmacovigilance legislation has put an increased emphasis on medication errors

- Explicitly considered in the Adverse Drug Reaction (ADR) definition of Directive 2001/83/EC
- Requirements for the collection and submission of information related to medication errors (EudraVigilance)
- Information available to patient safety organisations
- Regulatory tools for risk assessment and management (Periodic Safety Update Reports and EU Risk Management Plans)

For the sake of clarity, the definition of the term 'adverse reaction' should be amended to ensure that it covers noxious and unintended effects resulting not only from the authorised use of a medicinal product at normal doses, but also from medication errors and uses outside the terms of the marketing authorisation, including the misuse and abuse of the medicinal product.

European Union – Guidelines

In 2015 the EU regulatory network published two Good Practice Guides (GPG) on medication errors

- Intended to support the implementation of the legal provisions amongst the stakeholders involved in the reporting, evaluation and prevention of medication errors
- Improve quality of reporting and learning from medication errors for the benefit of public health
- Complementary to other EU and International guidelines as applicable (Good Pharmacovigilance Practice, ICH, MedDRA)

23 October 2015
EMA/762563/2014
Pharmacovigilance Risk Assessment Committee (PRAC)

Good practice guide on recording, coding, reporting and assessment of medication errors

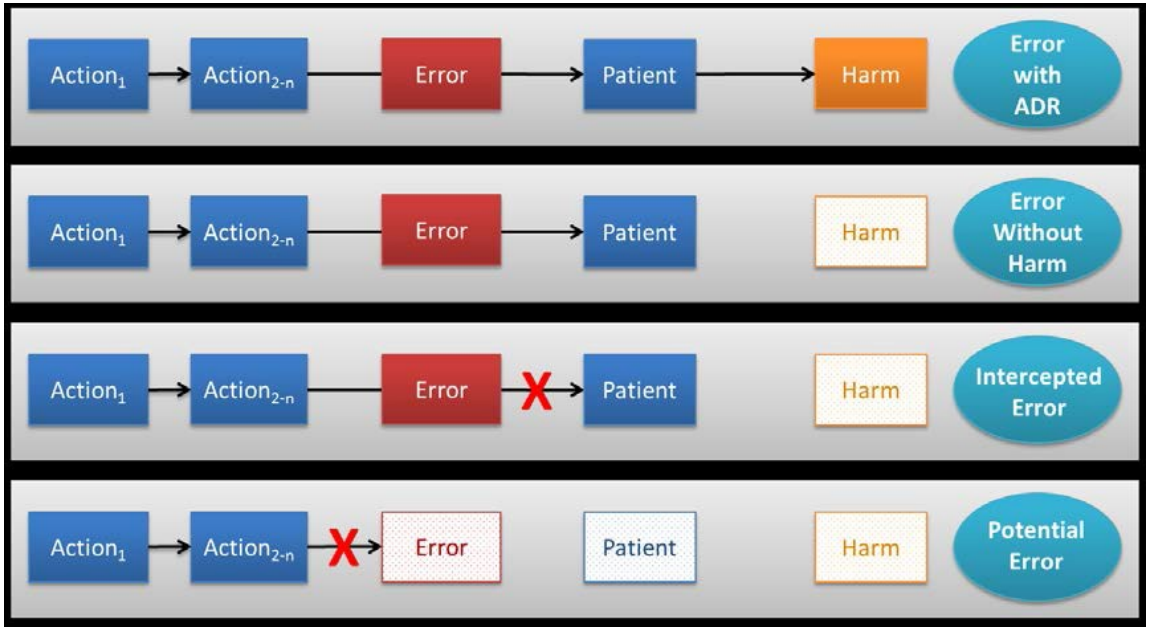
18 November 2015
EMA/606103/2014
Pharmacovigilance Risk Assessment Committee (PRAC)

Good practice guide on risk minimisation and prevention of medication errors

Medication error – definition

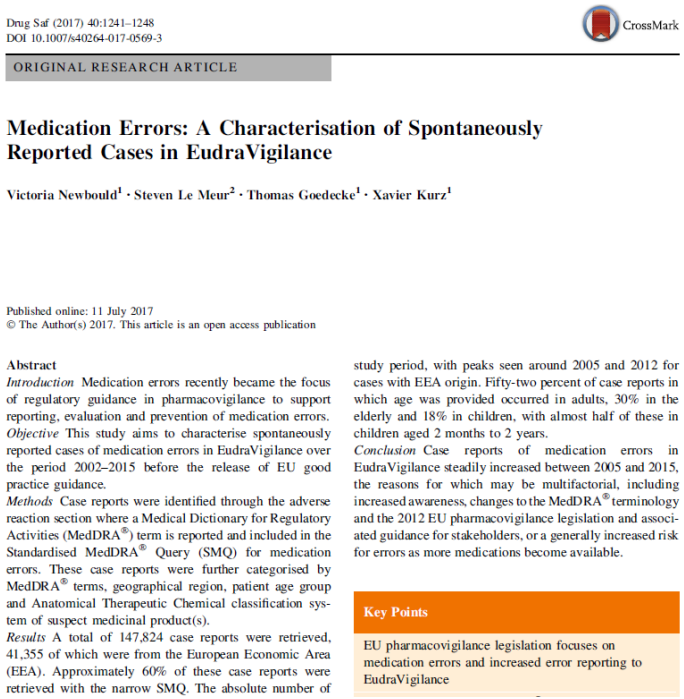
'A medication error is an unintended failure in the drug treatment process that leads to, or has the potential to lead to, harm to the patient.'

Medication errors – Classification



Characterisation of spontaneously reported cases in EudraVigilance

- Characterise spontaneously reported cases of medication errors to EudraVigilance (centralised European database for reporting and evaluating suspected ADRs to medicines authorised in the EEA)
- Study period: Jan 2002 – Dec 2015
- Spontaneous reports
- MedDRA SMQ for medications errors (Broad and Narrow) (MedDRA version 19.0)
- Categorisation by MedDRA Terms, geographical region, patient age group and Anatomical Therapeutic Chemical (ATC) classification system of suspect medicinal products



Drug Saf (2017) 40:1241–1248
DOI 10.1007/s40264-017-0569-3

CrossMark

ORIGINAL RESEARCH ARTICLE

Medication Errors: A Characterisation of Spontaneously Reported Cases in EudraVigilance

Victoria Newbould[1] · Steven Le Meur[2] · Thomas Goedecke[1] · Xavier Kurz[1]

Published online: 11 July 2017

Abstract

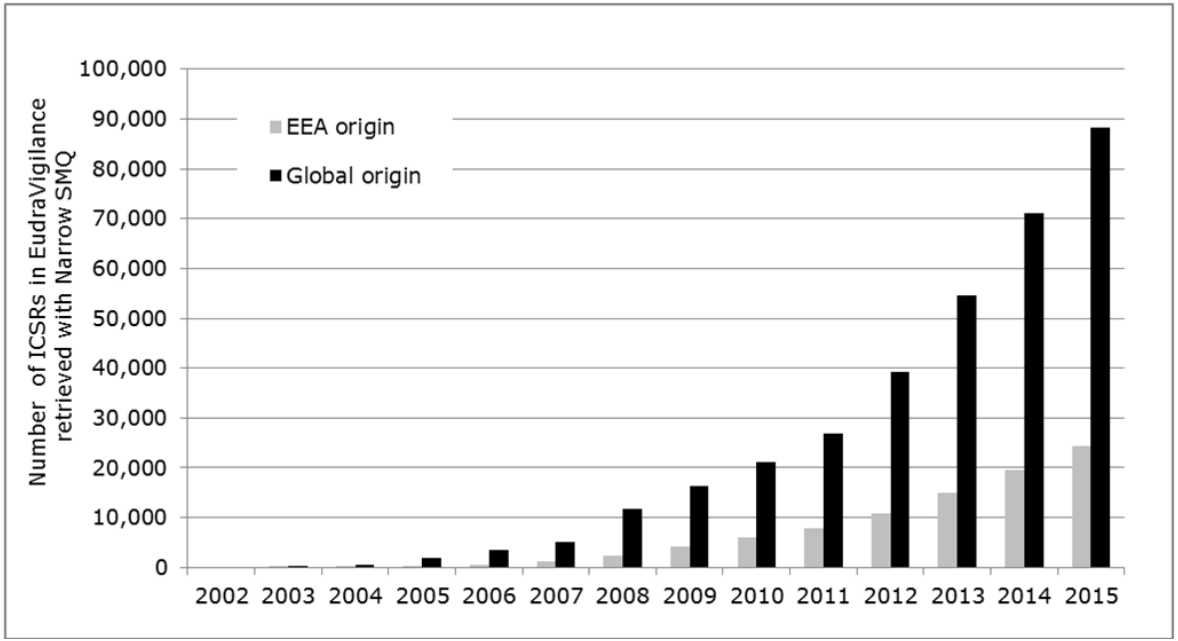
Introduction Medication errors recently became the focus of regulatory guidance in pharmacovigilance to support reporting, evaluation and prevention of medication errors.
Objective This study aims to characterise spontaneously reported cases of medication errors in EudraVigilance over the period 2002–2015 before the release of EU good practice guidance.
Methods Case reports were identified through the adverse reaction section where a Medical Dictionary for Regulatory Activities (MedDRA®) term is reported and included in the Standardised MedDRA® Query (SMQ) for medication errors. These case reports were further categorised by MedDRA® terms, geographical region, patient age group and Anatomical Therapeutic Chemical classification system of suspect medicinal product(s).
Results A total of 147,824 case reports were retrieved, 41,355 of which were from the European Economic Area (EEA). Approximately 60% of these case reports were retrieved with the narrow SMQ. The absolute number of study period, with peaks seen around 2005 and 2012 for cases with EEA origin. Fifty-two percent of case reports in which age was provided occurred in adults, 30% in the elderly and 18% in children, with almost half of these in children aged 2 months to 2 years.
Conclusion Case reports of medication errors in EudraVigilance steadily increased between 2005 and 2015, the reasons for which may be multifactorial, including increased awareness, changes to the MedDRA® terminology and the 2012 EU pharmacovigilance legislation and associated guidance for stakeholders, or a generally increased risk for errors as more medications become available.

Key Points

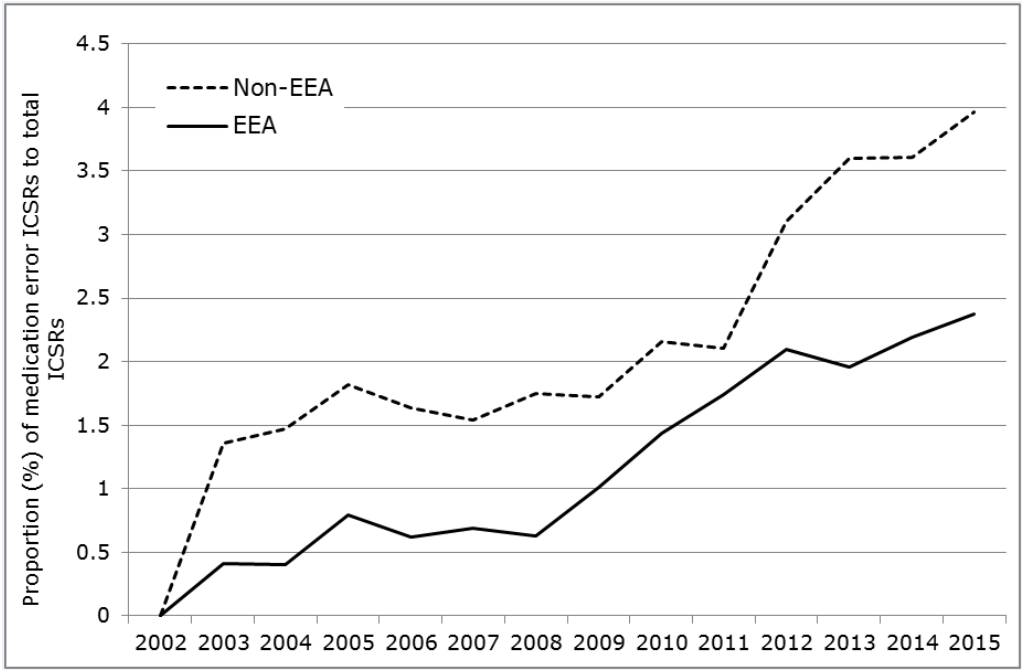
EU pharmacovigilance legislation focuses on medication errors and increased error reporting to EudraVigilance

Study results: Number of cases and cumulative figures

- Total of 147,824 case reports retrieved (Broad SMQ)
- 41,355 occurred in the EEA (Broad SMQ)
- The absolute number of medication errors case reports has been increasing over time

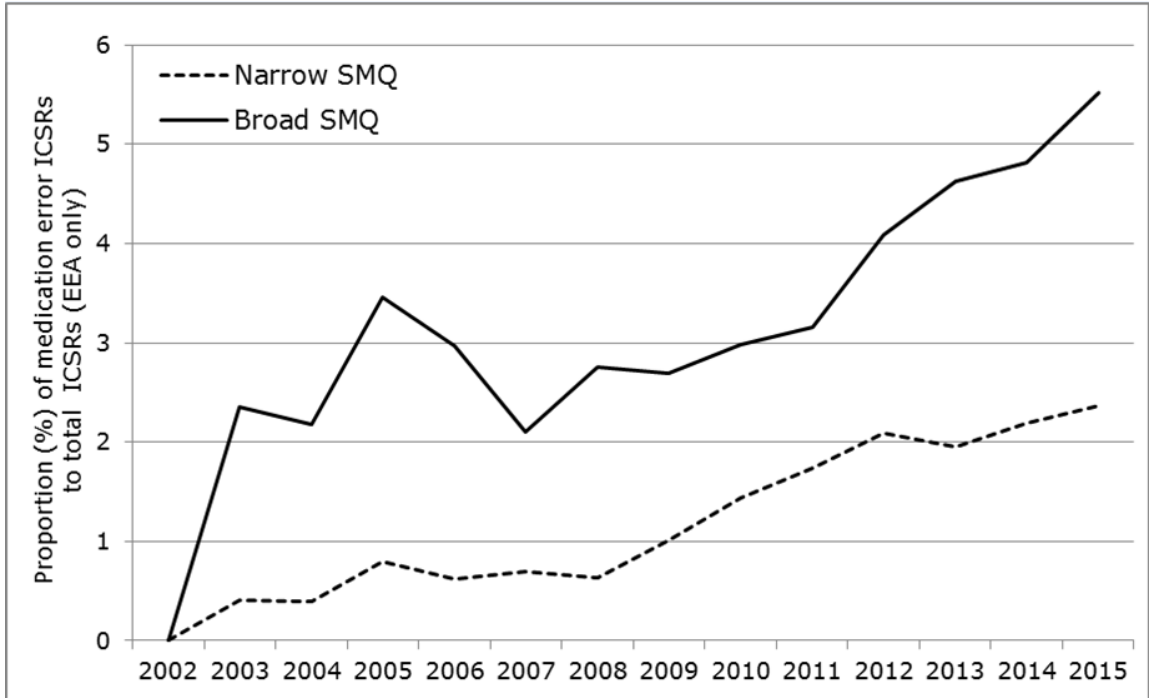


Study results: Proportion of cases EEA, non-EEA

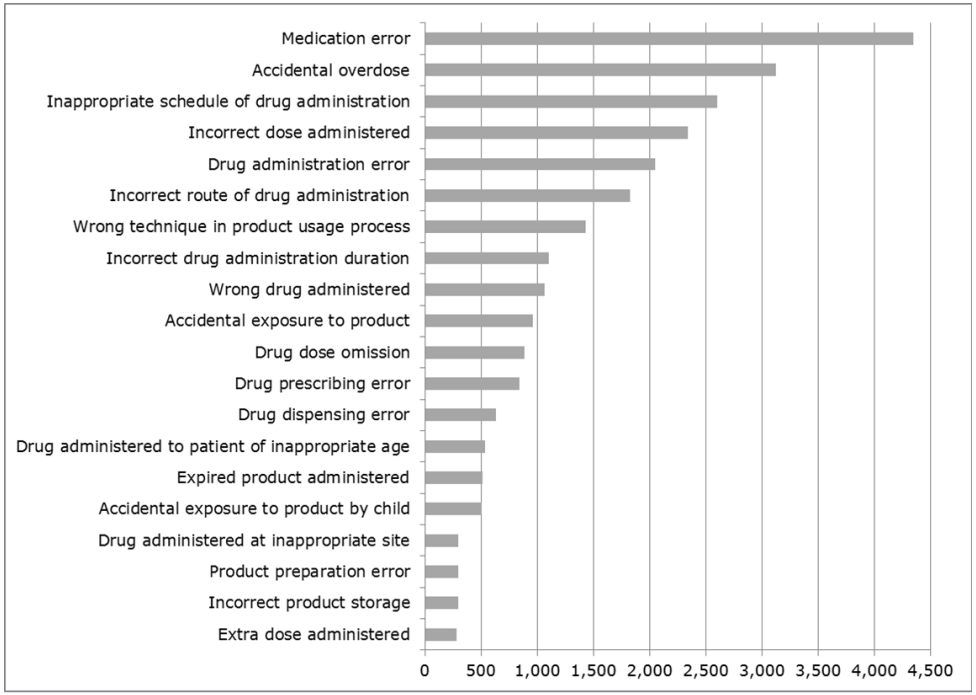


Study results: proportion of cases - EEA

- In the EEA, the proportion of medication errors to total number of ADR reports increased with peaks seen around 2005 (electronic reporting mandatory) using the Broad SMQ and 2012 (EU pharmacovigilance legislation) using the narrow SMQ



Study results: MedDRA Preferred Terms (PT) in the EEA



Study results: Ranking of ATC codes

- The most commonly reported MedDRA PT for vaccines is *'inappropriate schedule of drug administration'*
- *'Accidental overdose'* occurred most frequently with paracetamol, opiates and benzodiazepines
- *'Drug administration errors'* were most frequently reported with cisapride, insulin, fluticasone/salmeterol, fentanyl and salbutamol

Ranking	EEA	Non-EEA
1	J07 (Vaccines)	N02 (Analgesics)
2	N05 (Psycholeptics)	N05 (Psycholeptics)
3	N02 (Analgesics)	A10 (Drugs used in diabetes)
4	B01 (Antithrombotics)	B01 (Antithrombotics)
5	G03 (Sex hormones)	L04 (Immunosupressants)
6	N06 (Psychoanaleptics)	R03 (Obstructive airways disease)
7	A10 (Drugs used in diabetes)	N06 (Psychoanaleptics)
8	N03 (Antiepileptics)	G03 (Sex hormones)
9	L01 (Antineoplastics)	N03 (Antiepileptics)
10	J01 (Antibacterials for systemic use)	N07 (Other nervous system drugs)

2018 - Study in EudraVigilance

- Describe medication errors reporting trends in EudraVigilance **before and after** the publication of the EU Good Practice Guide (GPG)
- Use time series analysis to evaluate trend changes following the publication of the GPG
- Qualitative analysis to further investigate whether root cause analysis is possible with the information provided in the cases (based on selected products)

- Study period: January 2002 – December 2017
- Times series analysis: January 2013 - December 2017
  - Sufficient pre and post intervention time points for the time series analysis and covers the date of the publication of the Guide (30th Nov 2015)
- Spontaneous reports
- MedDRA SMQ medication errors narrow
- Categorisation by region of occurrence, primary source of report, seriousness criterion, age group and ATC code

Time series analysis

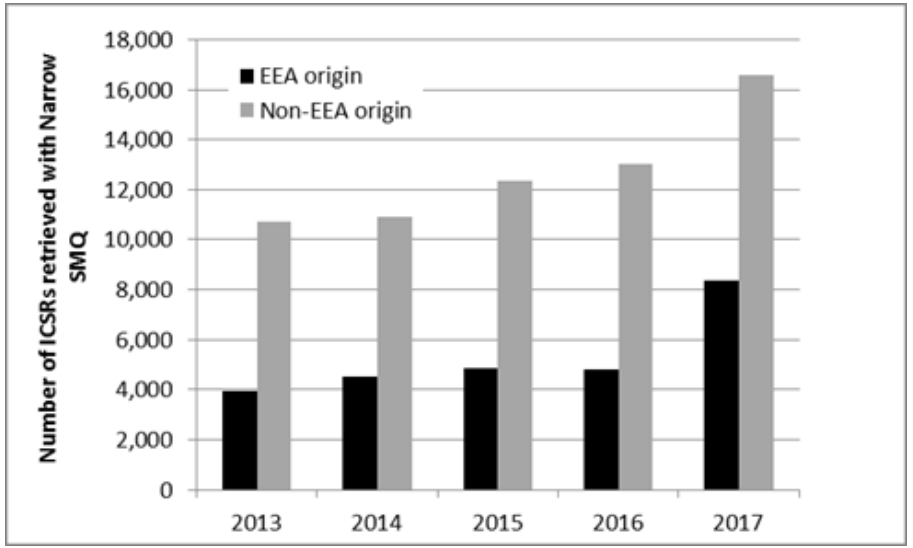
- Quarterly proportion of medication errors to the total number of cases
- Interrupted time series analysis with linear regression model to assess whether the underlying reporting trend has been affected by the intervention

➢ Concluded that the publication of the GPG in Nov 2015 was not associated with an immediate change in medication error reporting and was not associated with a significant change in post-intervention trend compare to the baseline

	Monthly Change (%)	95% CI	p-value
EEA reporting			
▪ Intercept	1.898	1.657 to 2.139	
▪ Baseline trend	0.015	0.004 to 0.027	0.011
▪ Immediate effect	0.080	-0.288 to 0.449	0.664
▪ Post-intervention trend	-0.008	-0.030 to 0.015	0.490
Non-EEA reporting			
▪ Intercept	3.376	3.186 to 3.567	
▪ Baseline trend	0.020	0.011 to 0.029	<0.001
▪ Immediate effect	-0.044	-0.336 to 0.248	0.764
▪ Post-intervention trend	-0.011	-0.029 to 0.007	0.236

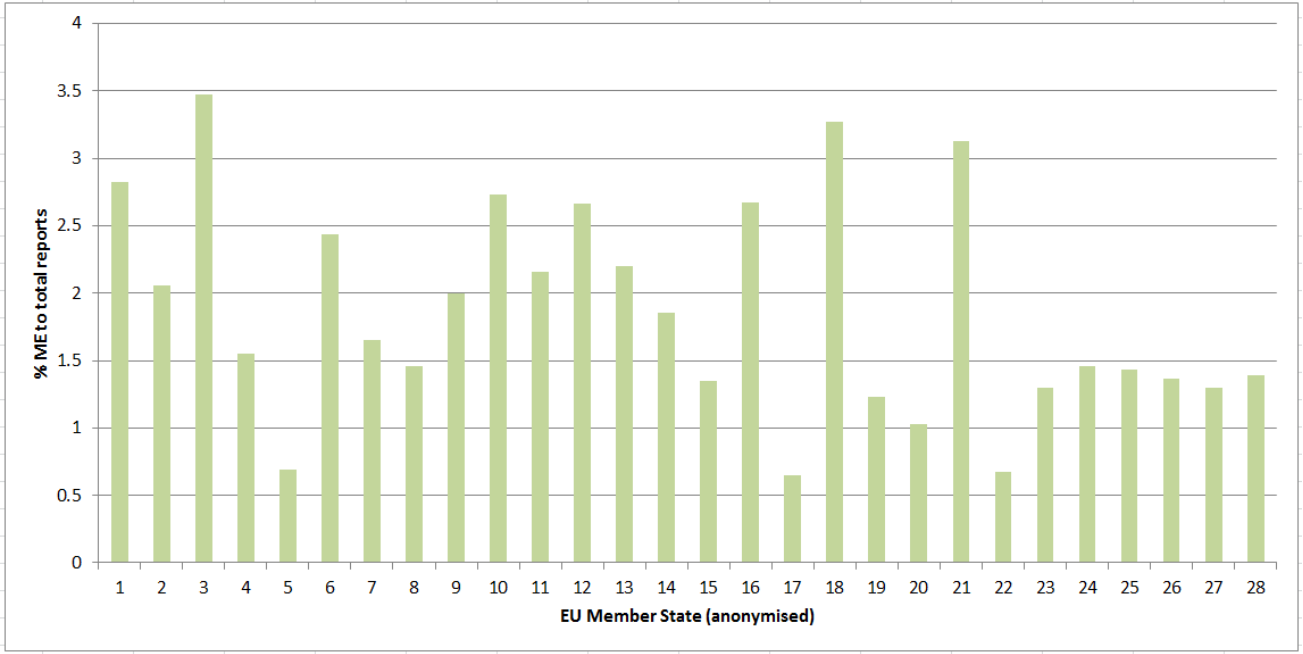
Some preliminary results on number of cases

- 128,392 cases were retrieved
- 2.59% of the total number of cases in EudraVigilance
- 29.05% originated within the EEA and 70.95% outside the EEA



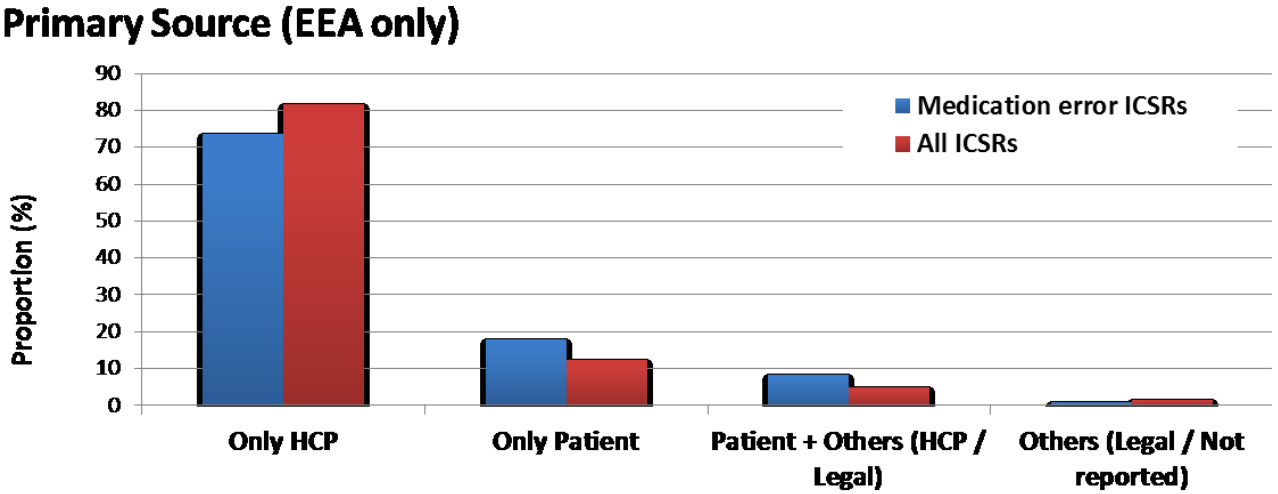
Variation of reporting rates per EU Member State

- National variations within the EU Member States
- Different legal requirements
- Differences in patient safety incidents reporting

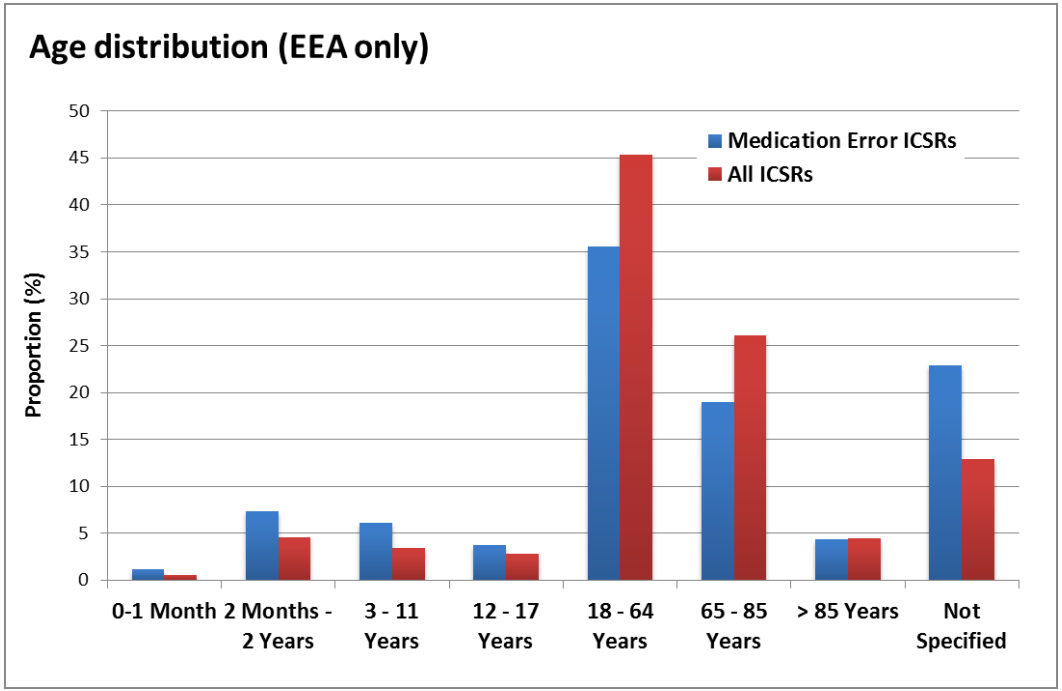


Primary source

- For patient reports the proportion of cases of medication errors is higher compared to all cases



Age distribution



Parameters for the qualitative evaluation of case reports

- Parameters to follow up when reporting medication errors (GPG Section 5.5.1)
- Contributing factors are particularly relevant for the analysis of route causes (e.g. human factors, communication issues, work environment, healthcare policies, etc.)

Case reports of medication errors should include where possible the following information:

- Classification of medication error
- Stage of medication process where the error occurred
- Contributing factor(s)
- Reported adverse reaction(s) if the error affected the patient or consumer with clinical consequences
- Potential for harm if a potential error or intercepted error did actually happen and reach the patient or consumer
- Medicinal product(s) involved
- Batch number if the error is due to device failure

Conclusions

- The reporting of cases of medication errors has been increasing between 2005 and 2015, both absolute numbers and proportion to all other reports in EudraVigilance.
- The synergy of different EU and international initiatives (public consultation of guidelines, SCOPE, communication of risk minimisation activities in relation to medication errors, activities related to MedDRA) has likely contributed to this increase and also to the granularity of coding.
- The release of the MedDRA SMQ for medication errors has been an important milestone to improve the detection and retrieval of reports related to medication errors.
- The proportion of medication errors vs the rest of the reports is higher in children than in adults.
- For patient reports, the proportion of cases of medication errors is higher compared to all cases.
- Ongoing further analysis to explore changes to the reporting trends of medication errors and the quality of reporting, considering all the different aspects (MedDRA evolvement, patient awareness, EU reporting requirements, publication of the EU guidelines, international initiatives).

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Further information

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Send a question via our website www.ema.europa.eu/contact

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Coding accuracy of administrative drug claims in the Ontario Drug Benefit database

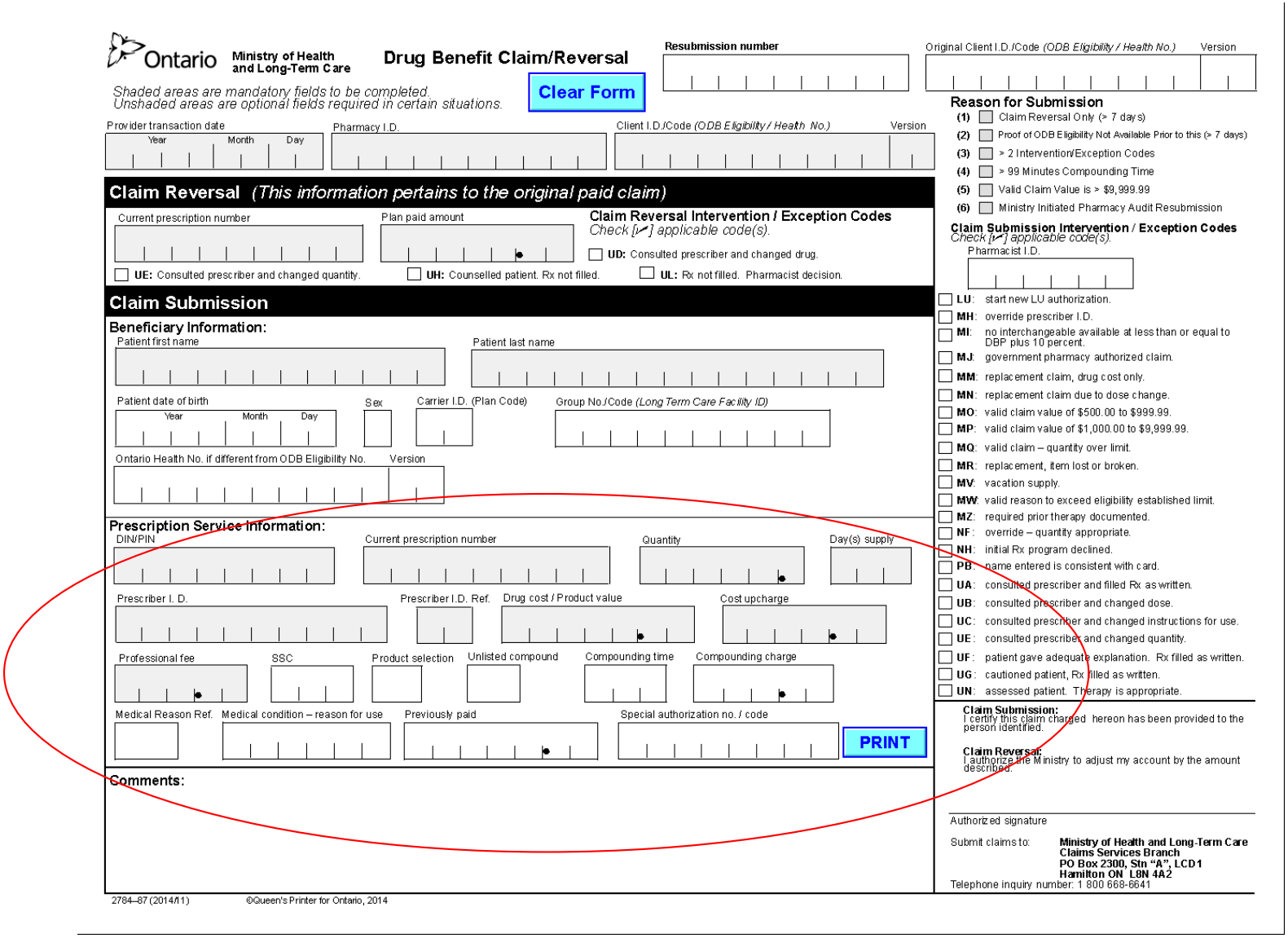
Adrian Levy PhD
Dalhousie University
Halifax, Nova Scotia, Canada

ADMINISTRATIVE HEALTH DATA

- Typically collected for reimbursement purposes
  - Standardized records of billable interactions between insured patients and care providers
  - Demographic/enrollment, inpatient/hospital, outpatient, pharmacy claims
- Very efficient for pharmacoepidemiology research
- Potentially key for distributed networks undertaking drug safety studies

ONTARIO DRUG CLAIMS DATABASE

- 160 million claims for 3.0 million Ontarians (2015)
  - 2.1 million aged ≥ 65 y
  - 0.9 million social assistance and others
- 8.8% of public expenditures on health (CDN$55B)
- 41% of all medications dispensed in Ontario
  - 2nd largest in Canada (after Quebec's RAMQ)
- Potentially excellent research resource provided data are reliable



Ontario Ministry of Health and Long-Term Care

Drug Benefit Claim/Reversal

Clear Form

Resubmission number | Original Client I.D./Code *(ODB Eligibility / Health No.)* | Version

Shaded areas are mandatory fields to be completed.
Unshaded areas are optional fields required in certain situations.

Provider transaction date (Year / Month / Day) | Pharmacy I.D. | Client I.D./Code *(ODB Eligibility / Health No.)* | Version

Reason for Submission

(1) ☐ Claim Reversal Only (> 7 days)
(2) ☐ Proof of ODB Eligibility Not Available Prior to this (> 7 days)
(3) ☐ > 2 Intervention/Exception Codes
(4) ☐ > 99 Minutes Compounding Time
(5) ☐ Valid Claim Value is > $9,999.99
(6) ☐ Ministry Initiated Pharmacy Audit Resubmission

Claim Reversal *(This information pertains to the original paid claim)*

Current prescription number | Plan paid amount

Claim Reversal Intervention / Exception Codes
Check [✓] applicable code(s).

☐ **UD:** Consulted prescriber and changed drug.
☐ **UE:** Consulted prescriber and changed quantity.
☐ **UH:** Counselled patient. Rx not filled.
☐ **UL:** Rx not filled. Pharmacist decision.

Claim Submission

Beneficiary Information:

Patient first name | Patient last name

Patient date of birth (Year / Month / Day) | Sex | Carrier I.D. (Plan Code) | Group No./Code *(Long Term Care Facility ID)*

Ontario Health No. if different from ODB Eligibility No. | Version

Prescription Service Information:

DIN/PIN | Current prescription number | Quantity | Day(s) supply

Prescriber I. D. | Prescriber I.D. Ref. | Drug cost / Product value | Cost upcharge

Professional fee | SSC | Product selection | Unlisted compound | Compounding time | Compounding charge

Medical Reason Ref. | Medical condition – reason for use | Previously paid | Special authorization no. / code

PRINT

Comments:

Claim Submission Intervention / Exception Codes
Check [✓] applicable code(s).

Pharmacist I.D.

☐ **LU:** start new LU authorization.
☐ **MH:** override prescriber I.D.
☐ **MI:** no interchangeable available at less than or equal to DBP plus 10 percent.
☐ **MJ:** government pharmacy authorized claim.
☐ **MM:** replacement claim, drug cost only.
☐ **MN:** replacement claim due to dose change.
☐ **MO:** valid claim value of $500.00 to $999.99.
☐ **MP:** valid claim value of $1,000.00 to $9,999.99.
☐ **MQ:** valid claim – quantity over limit.
☐ **MR:** replacement, item lost or broken.
☐ **MV:** vacation supply.
☐ **MW:** valid reason to exceed eligibility established limit.
☐ **MZ:** required prior therapy documented.
☐ **NF:** override – quantity appropriate.
☐ **NH:** initial Rx program declined.
☐ **PB:** name entered is consistent with card.
☐ **UA:** consulted prescriber and filled Rx as written.
☐ **UB:** consulted prescriber and changed dose.
☐ **UC:** consulted prescriber and changed instructions for use.
☐ **UE:** consulted prescriber and changed quantity.
☐ **UF:** patient gave adequate explanation. Rx filled as written.
☐ **UG:** cautioned patient, Rx filled as written.
☐ **UN:** assessed patient. Therapy is appropriate.

Claim Submission:
I certify this claim charged hereon has been provided to the person identified.

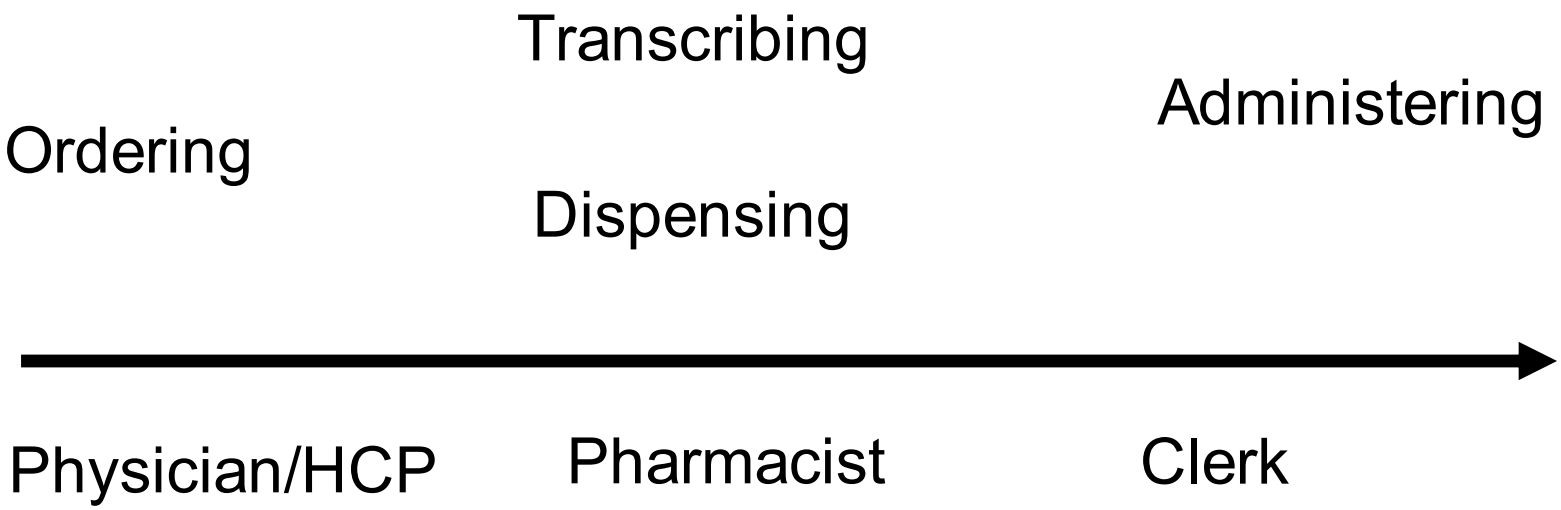
Claim Reversal:
I authorize the Ministry to adjust my account by the amount described.

Authorized signature

Submit claims to: **Ministry of Health and Long-Term Care**
Claims Services Branch
PO Box 2300, Stn "A", LCD1
Hamilton ON L8N 4A2
Telephone inquiry number: 1 800 668-6641

2784–87 (2014/11)

Key message: understand the process underlying the data



WHAT'S LURKING BEHIND A DRUG CLAIM?

OBJECTIVE

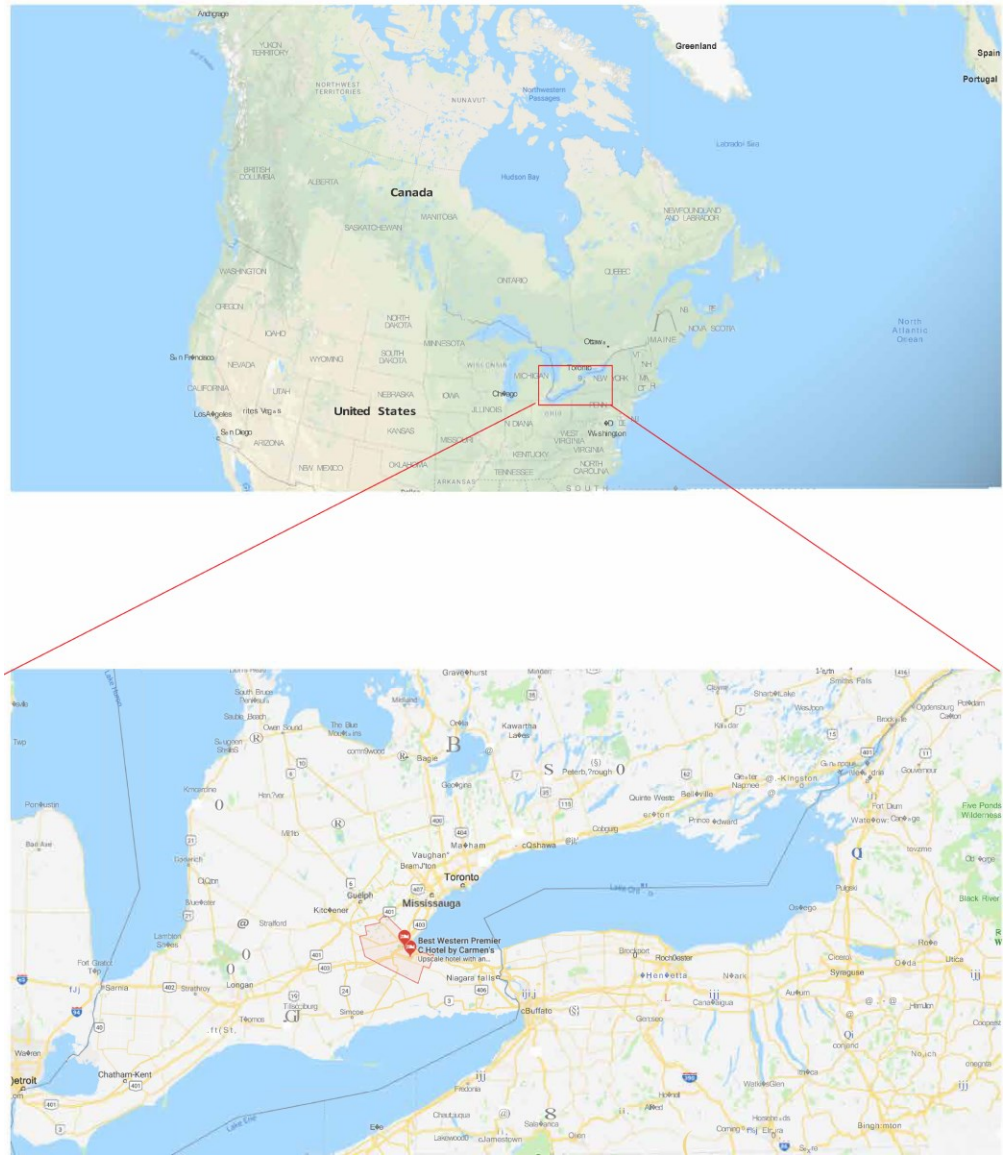
- To estimate the reliability of coding of the Drug Identification Number, and the date, quantity and duration of the dispensation on medication claims sent to the Ontario Drug Benefit database

HYPOTHESIS

- Coding errors would be more likely to occur among pharmacies having higher volume

  ➔ less time per prescription

- Also examined: location, owner affiliation


Canada
United States
Greenland
Spain
Portugal
Toronto
Mississauga
Best Western Premier
Hotel by Carmen's
Niagara Falls
Chatham-Kent

DESIGN

- Randomly chose dispensed medications from different months in 1999

- Compared written prescription with label

- Information
  - date, drug identification number, quantity of drug
  - prescriber - type, location
  - pharmacy's "productivity"

PHARMACIES

	n	%	N invited	% participation
ANCASTER	6	12	6	100
BURLINGTON	7	14	40	17
HAMILTON	19	38	26	73
ST CATHERINES	10	20	13	77
TORONTO	8	16	99	8

PRESCRIPTIONS DISPENSED

Pharmacologic-Therapeutic Classification	n	%
28:00 Anti-infective agents	1399	27
8:00 Central nervous system drugs	1287	25
24:00 Cardiovascular medications	965	19
68:00 Hormones and substitutes	425	8
56:00 Gastrointestinal drugs	373	7
All other	706	14
All	**5155**	**100**

MAIN RESULT

5,155 Dispensed Prescriptions, 37 Errors

➔ overall error rate = 0.7% (95% CI = 0.5% to 0.9%)

- 13 - Rx had something other than prescribed
- 11 - identified the wrong physician
- 9 - errors in the instructions to the patient
- 4 – clerical, affecting information sent to ODB

HYPOTHESIS

- coding errors would be more likely to occur among pharmacies having higher volume (less time per Rx)

- using logistic regression: none of the characteristics of pharmacies (location, owner affiliation, productivity) were associated with coding errors

➔ low power to detect differences

LIMITATIONS

- Biggest threat to validity: selection bias

was it the pharmacies with “better” coding practices that participated?

- Could not examine:

- all sources of coding errors
- patient characteristics, time of day
- prescribing, dispensing, or administering

EVIDENCE FROM THIS STUDY

➔ claims are reliabl transcriptions of information listed on prescriptions

➔ inferences drawn using drug claims data are not likely to be compromised by low reliability of coding