Accumulated wisdom from 3 decades of pre- and postmarket safety review in FDA's Center for Drug Evaluation and Research (CDER)

Judith A. Racoosin, MD, MPH

(recently retired from FDA)

October 8, 2025

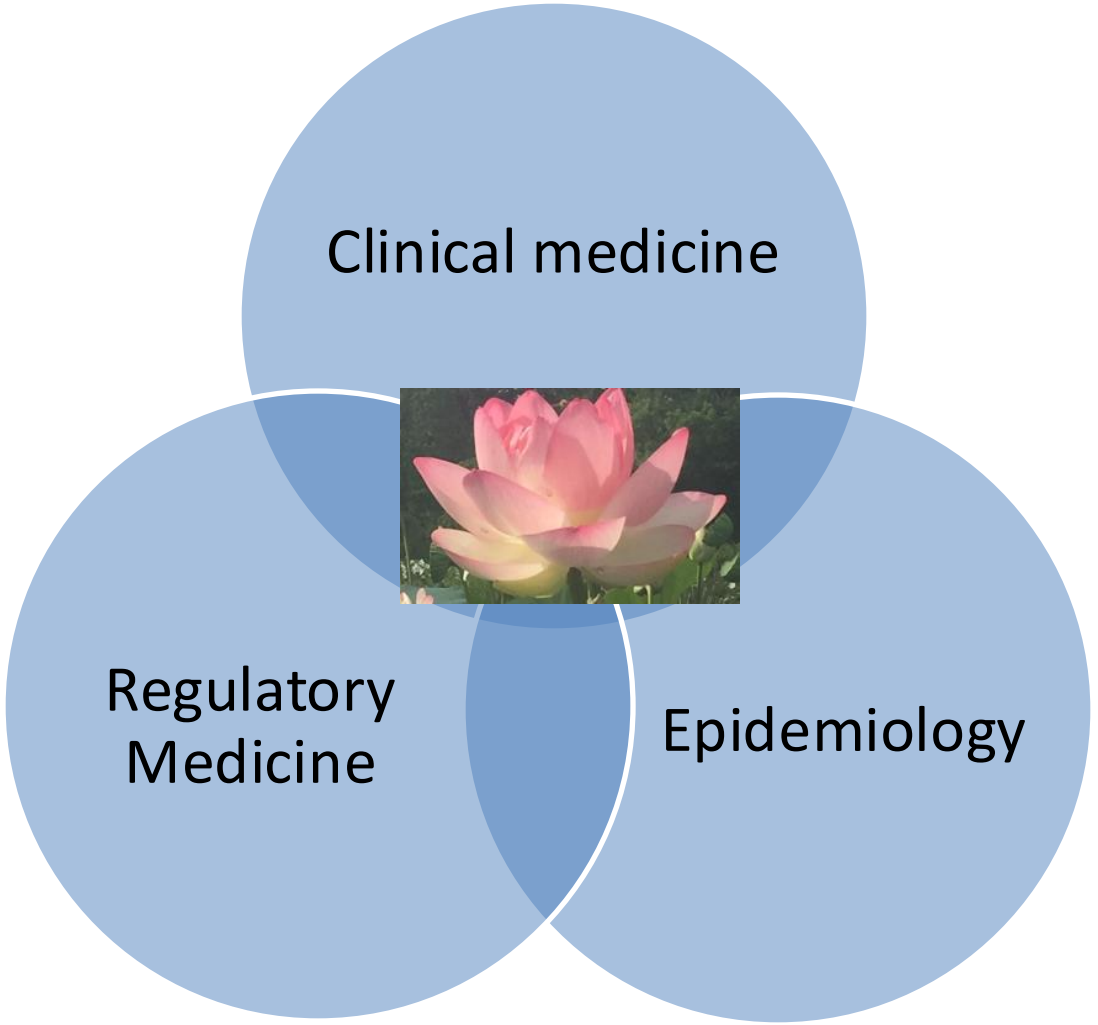
Disclaimer

- The material I am covering is my perspective and does not reflect the official position of the US Food and Drug Administration (FDA).

My FDA Journey

Aug 1995 – April 1997	US Public Health Service Epidemiology Training Program	MPH- U of Illinois at Chicago Office of Pharmacovigilance and Epidemiology/ Epidemiology Branch (Parklawn)
April 1997 – March 2000	Office of Review Management/ Division of Neuropharmacological Drug Products	Medical Officer (Woodmont II)
March 2000 – June 2006	Office of New Drugs (OND)/ Division of Neuropharmacological Drug Products	Safety Team Leader (Woodmont II, White Oak [WO] 22)
June 2006 – Feb 2009	Office of the Center Director - Safety Policy and Communication Staff	Senior Safety Policy Advisor (Rockwall, WO51)
Feb 2009 – Sept 2011	Office of the Commissioner CDER/ Office of Medical Policy	Sentinel Initiative Scientific Lead (Parklawn, WO51)
Sept 2011 – May 2020	OND/ Division of Anesthesia, Analgesia, and Addiction Products	Deputy Director for Safety (WO22)
May 2020 – Aug 2025	OND/ Division of Hepatology and Nutrition	Deputy Director for Safety (Home, WO22)

At the nexus…



Accumulated Wisdom

- Drug safety is a collaborative effort.
- We accomplish more with postmarket safety authorities.
- Data and analytic tools are essential.
- We can prevent some medication errors.
- We can warn about idiosyncratic side effects.
- We must protect our most vulnerable populations.
- We must communicate to stakeholders.
- Drug safety is important, but we must consider it in the context of benefit.

Everyone in CDER contributes to the understanding of drug safety

Office of Executive Programs

Planned many Advisory Comm mtgs

Office of Communications

Collaborated on many
Drug Safety Communications

Office of Pharmaceutical Quality

Phytosterols workshop
Elemental impurities

Office of Management

Contract management-
"Mini-sentinel"

Office of New Drugs ★
3 divisions totaling 23 yrs

Office of Strategic Programs

Benefit/Risk framework

Office of Surveillance and Epidemiology 9 mos ★

Collaborations too numerous to mention

Office of the Center Director 2.5 yrs ★

Collabs with Drug Safety Operations
and the Controlled Substances Staff

Office of Medical Policy 2.5 yrs ★

Patient Labeling
Real World Data/Evidence

Office of Translational Sciences

Pharmacogenomic issues with codeine
Methemoglobinemia RBC study

Office of Compliance

Safety issue- marketed unapproved Kphos
"Untitled letter" for tramadol postmarket requirement (PMR) noncompliance

Office of Generic Drugs

Many Safety Labeling Change actions
Aluminum toxicity with parenteral products

Office of Regulatory Policy

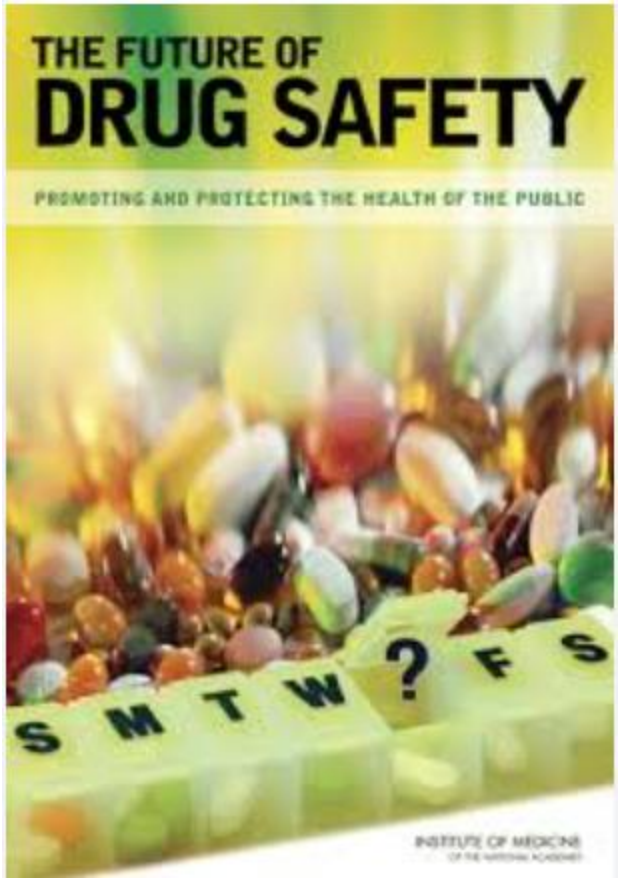
FDA Amendments Act of 2007 Implementation
Citizen's petitions – codeine, others
Guidance development

★ Where I worked

Accumulated Wisdom

- Drug safety is a collaborative effort.
- We accomplish more with postmarket safety authorities.
- Data and analytic tools are essential.
- We can prevent some medication errors.
- We can warn about idiosyncratic side effects.
- We must protect our most vulnerable populations.
- We must communicate to stakeholders.
- Drug safety is important, but we must consider it in the context of benefit.

The Institute of Medicine Report (September 2006)



The Future of Drug Safety: Promoting and Protecting the Health of the Public

Committee on the Assessment of the US Drug Safety System, Alina Baciu, Kathleen Stratton, Sheila P. Burke, Editors

ISBN: 0-309-10304-5, 350 pages, 6 x 9, hardback (2006)

Food and Drug Administration Amendments Act of 2007 (FDAAA)

- Title I – PDUFA
- Title II – MDUFMA
- Title III – Peds Devices
- Title IV – PREA
- Title V – BPCA
- Title VI – Reagan/Udall
- Title VII - COI
- Title VIII – Clinical Trials Database
- Title IX – Postmarket Drug Safety
- Title X – Food Safety
- Title XI – Misc. Provisions

FDAAA Title IX – Drug Safety

- New authorities to:
  - **Require** pharmaceutical companies to conduct postmarketing studies and clinical trials to investigate safety concerns
  - **Require** pharmaceutical companies to make safety-related labeling changes
  - **Require** pharmaceutical companies to develop and comply with risk evaluation and mitigation strategies (REMS)

Example of use of postmarket safety authorities: Smoking cessation drugs and neuropsychiatric side effects

- Chantix (varenicline) approved May 2006
- Zyban (bupropion) approved May 1997
- Safety signal for neuropsychiatric side effects emerged mid-2007
  - Examples: changes in mood (including depression and mania), psychosis, hallucinations, paranoia, delusions, homicidal ideation, aggression, hostility, agitation, anxiety, and panic, as well as suicidal ideation, suicide attempt, and completed suicide

Safety Authority	Date	Action
Risk Evaluation and Mitigation Strategy (REMS)	May 2008 (Chantix) Feb 2009 (Zyban)	Medication Guide and Communication Plan
Postmarket Requirement (PMR)	May 2008 (Chantix) Feb 2009 (Zyban)	March 2010 finalized PMR description and milestone dates for placebo- and active-controlled randomized controlled trial
Safety Labeling Change (SLC)	July 2009 (Chantix and Zyban)	Boxed Warning required; changes to other sections of labeling as well

2014 Psychopharmacologic Drugs Advisory Committee (PDAC) discussion

- The Division reviewed information that was submitted by the Applicant and revised the Chantix (varenicline) labeling (Warnings and Precautions section) in Sept 2014 so that prescribers could have a full picture of what meta-analyses and observational studies had been conducted to enhance the understanding of varenicline-associated serious neuropsychiatric adverse events.
- There was no precedent for the determining what robustness of data was needed to support removal of a boxed warning, leading to the FDA convening a PDAC discussion in Oct 2014.
- 65% of the PDAC members (11/17) voted to delay potential removal of the boxed warning until the results of the ongoing randomized controlled trial were available, citing uncertainties about outcome ascertainment of neuropsychiatric side effects in the observational studies, among other concerns

Smoking cessation drugs and neuropsychiatric side effects: post-PMR trial PDAC discussion (2016)

- PMR findings
  - Incidence of clinically significant neuropsychiatric adverse events were similar across treatment groups in both non-psychiatric and psychiatric cohorts
  - In both cohorts, patients treated with Chantix, Zyban, or nicotine patch had a superior rate of CO-confirmed abstinence during weeks 9 through 12 and weeks 9 through 24 compared to patients treated with placebo
- Regulatory action
  - Boxed warning removed from Chantix and Zyban labeling
  - W/P statement on neuropsychiatric adverse events revised
  - REMS requirement removed, although the MedGuide remained

Accumulated Wisdom

- Drug safety is a collaborative effort.
- We accomplish more with postmarket safety authorities.
- Data and analytic tools are essential.
- We can prevent some medication errors.
- We can warn about idiosyncratic side effects.
- We must protect our most vulnerable populations.
- We must communicate to stakeholders.
- Drug safety is important, but we must consider it in the context of benefit.

Using premarket data to evaluate class safety issues

Example 1: Mortality with newer antiepileptic drugs

Mortality in antiepileptic drug development programs

Judith A. Racoosin, MD, MPH; John Feeney, MD; Greg Burkhart, MD, MS; and Gerard Boehm, MD, MPH

Article abstract—*Background:* Pooled data from New Drug Applications (NDAs) submitted to the U.S. Food and Drug Administration (FDA) provide an opportunity to study the incidence of and risk factors for rare events. *Objective:* To examine the incidence and causes of mortality in patients with epilepsy participating in clinical trials of antiepileptic drugs (AEDs); and to examine the incidence of and risk factors for sudden unexplained death in such patients. *Methods:* Exposure data and death narratives were obtained from the NDAs of five recently reviewed AEDs. Deaths were classified as sudden unexplained, accidental, or other cause using the 1993 Burroughs–Wellcome expert panel criteria, and mortality rates were calculated for each category. Add-on trials were analyzed separately from monotherapy initiation trials. *Results:* Among 9,144 patients in the add-on trial database, the all-cause and sudden unexplained mortality rates were 9.1 and 3.8 deaths per 1,000 person-years (124 and 52 deaths in 13,617.1 person-years of drug exposure). Sixty-five percent of all deaths were related to the underlying epilepsy. Of the examined risk factors, only age was associated with the incidence of sudden unexplained death. Among 1,293 patients in the monotherapy initiation trials, the all-cause and sudden unexplained mortality rates were 7.1 and 0 deaths per 1,000 person-years (7 and 0 deaths in 982.5 person-years of drug exposure). *Conclusions:* A large proportion of the deaths in the add-on cohort was attributable to epilepsy-related causes. Mortality due to sudden death in the add-on cohort falls into the high end of the reported range for patients with epilepsy. The difference in mortality due to sudden death between the add-on and monotherapy initiation cohorts suggests that disease severity is the primary determining factor for risk of sudden unexplained death.

NEUROLOGY 2001;56:514–519

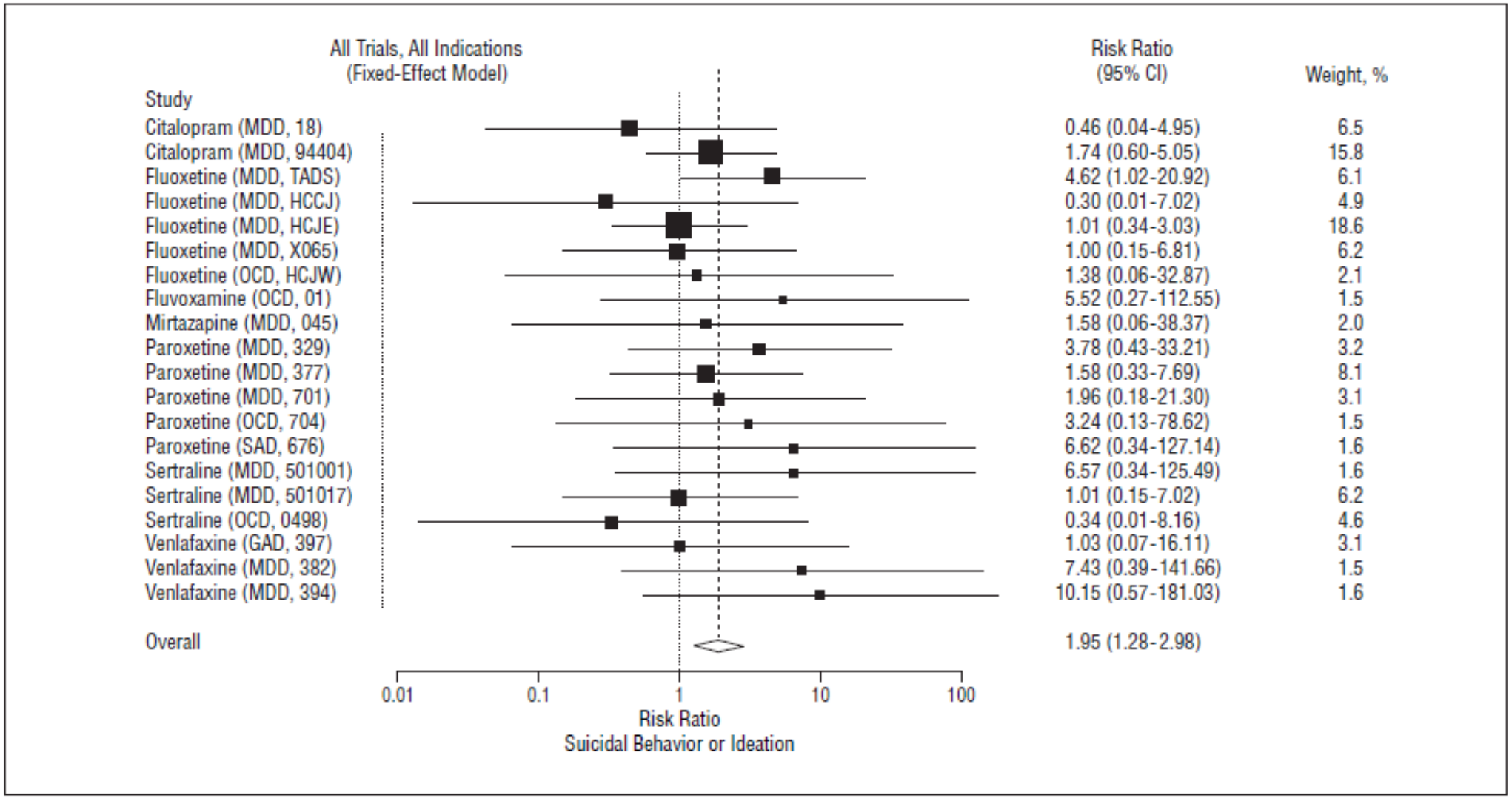
Using premarket data to evaluate class safety issues

Example 2: Pediatric suicidality with the antidepressants*

- The Division of Neuropharmacological Drug Products asked manufacturers of the 9 antidepressant drugs to search their databases to identify adverse events that might potentially represent suicidal ideation or behavior
- All potential case narratives were independently and blindly classified into relevant categories by a group of 10 pediatric suicidology experts assembled by Columbia University to provide as much assurance as possible that cases had been appropriately classified
- Meta analysis conducted
  - Results presented to Psychopharmacologic Drugs Advisory Committee Sept 2004
- Class boxed warning added

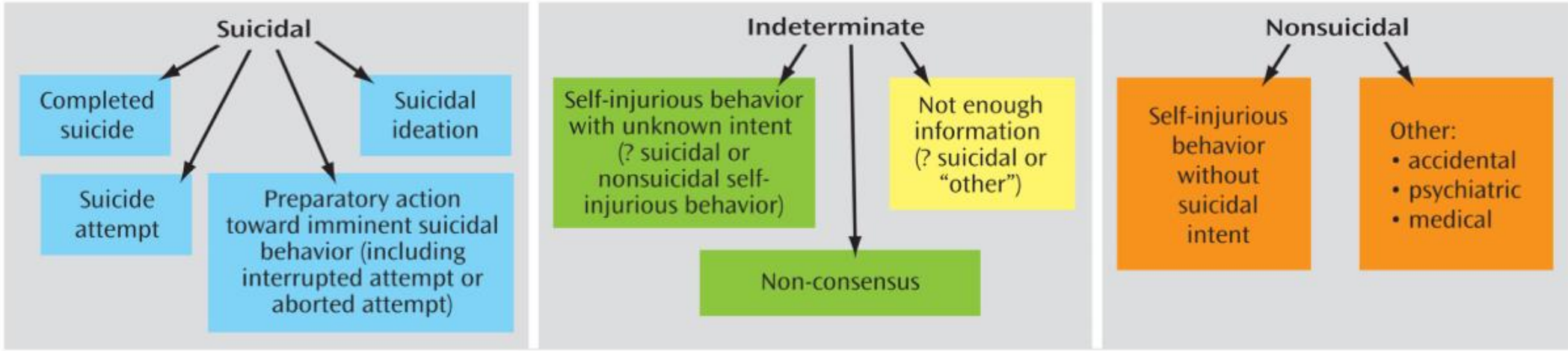
*Hammad TA, et al. Arch Gen Psychiatry 2006

Risk ratio for suicidal behavior or ideation



*Hammad TA, et al. Arch Gen Psychiatry 2006

Columbia Classification Algorithm for Suicide Assessment (C-CASA) Suicidality classification scheme*



C-CASA Definitions and Training Examples

Importance of phenotyping!

Classification/ Category	Definition	Training Examples
Suicidal events Completed suicide	A self-injurious behavior that resulted in fatality and was associated with at least some intent to die as a result of the act.	1) After a long argument with his girlfriend, which resulted in the end of their relationship, the patient collected a rope and rode his bike to an isolated area where he fatally hanged himself. A suicide note was later found. 2) After four documented attempts at suicide, the patient stole his uncle's gun and shot himself and was fatally injured.
Suicide attempt	A potentially self-injurious behavior, associated with at least some intent to die, as a result of the act. Evidence that the individual intended to kill him/ herself, at least to some degree, can be explicit or inferred from the behavior or circumstance. A suicide attempt may or may not result in actual injury.	1) After a fight with her friends at school, in which they discontinued speaking with her, the patient ingested approximately 16 aspirin and eight other pills of different types on the school grounds. She said that she deserved to die, which was why she swallowed the pills. 2) The patient used a razor blade to lacerate his wrists, his antecubital fossae, and his back bilaterally. He told his therapist that the "the main objective was to stop feeling like that," and he knew that he could die but didn't care. According to the patient, he also ingested a bottle of rubbing alcohol because in his health class he heard "that the medulla will get more suppressed that way," thereby increasing the chances that he would be "successful" and die.

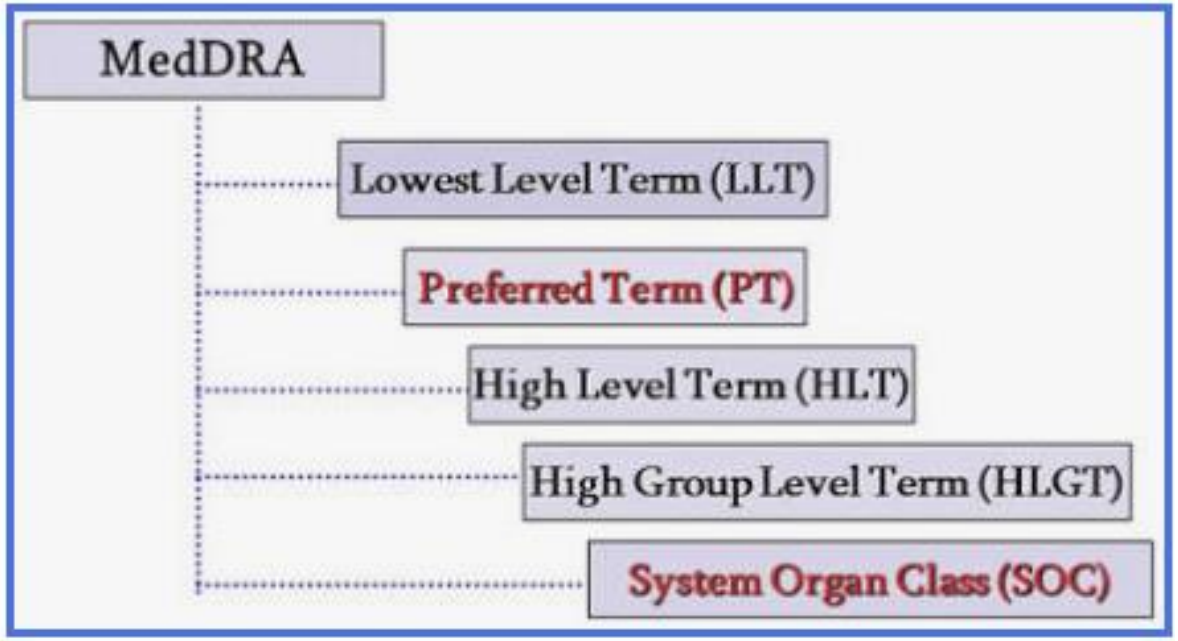
*Posner et al. Am J Psychiatry 2007

Guidance for Industry: Suicidal ideation and behavior (2012)

- Assist sponsors in prospectively assessing the occurrence of treatment-emergent suicidal ideation and behavior in clinical trials of drug and biological products.
- Recommend actively querying patients about the occurrence of suicidal thinking and behavior, rather than relying on patients to report such occurrences spontaneously, followed by retrospective classification of events into appropriate categories
- Criteria that should be met for a suicidal ideation and behavior assessment instrument that can be used to conduct such prospective assessments

Use of MedDRA in Pre-Market Safety Review
importance of standardized vocabularies

- Medical Dictionary for Regulatory Activities
- Validated international medical terminology
- Used through entire regulatory process
- Sound knowledge of MedDRA is critical for conducting effective safety review
  - Safety signals can be missed
  - Lumping vs. splitting



meddra.org

How Can a Signal Be Missed?

• Perform analyses on different levels of the MedDRA hierarchy

- Preferred Term
  - Vision blurred 2/200 (1.0%)
  - Visual disturbance 2/200 (1.0%)
  - Diplopia 1/200 (0.5%)
  - Vision abnormal 1/200 (0.5%)
  - Visual acuity reduced 1/200 (0.5%)
  - Presbyopia 1/200 (0.5%)

- High Level Group Term
  - Vision Disorders
    - 8/200 (4%)

All of these PT terms map to Vision Disorders. An AE analysis of Vision Disorders shows a higher percentage of events and appears higher up in a table sorted according to frequency

Tools for postmarket safety review

FDA Amendments Act (FDAAA) of 2007

Sec. 905. Active Postmarket Risk Identification and Analysis

(B) DEVELOPMENT OF POSTMARKET RISK IDENTIFICATION AND ANALYSIS METHODS.

The Secretary shall, not later than 2 years after the date of the enactment of the Food and Drug Administration Amendments Act of 2007, in collaboration with public, academic, and private entities—

(i) **develop methods to obtain access to disparate data sources** including the data sources specified in subparagraph (C);

(ii) develop validated methods for the **establishment of a postmarket risk identification and analysis system** to link and analyze safety data from multiple sources, with the goals of including, in aggregate—

(I) at least 25,000,000 patients by July 1, 2010; and

(II) at least 100,000,000 patients by July 1, 2012

Early days of the Sentinel Initiative

- Mini-Sentinel→ data core, methods core, clinical core.
  - Evolved into the current Sentinel Operations Center and the Sentinel Innovation Center (sentinelinitiative.org)
- Federal Partners Collaboration
  - CMS, VA, DoD, FDA collaborated on shared safety concerns
  - Example: Mosholder A, et al. Bleeding Events Following Concurrent Use of Warfarin and Oseltamivir by Medicare Beneficiaries. Annals of Pharmacotherapy 2013.
- Observational Medical Outcomes Partnership (OMOP)
  - A public- private partnership between FDA and Pharma to develop data infrastructure and methods for medical product safety surveillance
  - In 2013, evolved into OHDSI (Observational Health Data Sciences and Informatics; ohdsi.org)

Accumulated Wisdom

- Drug safety is a collaborative effort.
- We accomplish more with postmarket safety authorities.
- Data and analytic tools are essential.
- We can prevent some medication errors.
- We can warn about idiosyncratic side effects.
- We must protect our most vulnerable populations.
- We must communicate to stakeholders.
- Drug safety is important, but we must consider it in the context of benefit.

Institute of Medicine report: "To Err is Human" (1999)

- Focused on preventable medical errors
  - 44,000 to 98,000 deaths/year due to medical errors
- Medical errors can be defined as the failure of a planned action to be completed as intended or the use of a wrong plan to achieve an aim.
- Among the problems that commonly occur during the course of providing health care are
  - adverse drug events,
  - improper transfusions,
  - surgical injuries and wrong-site surgery,
  - restraint-related injuries or death,
  - falls,
  - burns,
  - pressure ulcers, and
  - mistaken patient identities.

http://www.iom.edu/~/media/Files/Report%20Files/1999/To-Err-is-Human/To%20Err%20is%20Human%201999%20%20report%20brief.pdf

Safe Use Initiative launched 2009

Safe Use Initiative

Collaborating to Reduce Preventable Harm from Medications

Today, tens of millions of people in the United States depend on prescription and OTC medications to sustain their health—more than four billion prescriptions are written annually. Too many people, however, suffer unnecessary injuries, and some die as a result of preventable medication errors. The U.S. Food and Drug Administration (FDA) believes that many of these medication-related risks are manageable if parties committed to the safe use of medications work together.

The mission of the *Safe Use Initiative* is to create and facilitate public and private collaborations within the healthcare community. The goal of the *Safe Use Initiative* is to reduce preventable harm by identifying specific, preventable medication risks and developing, implementing and evaluating cross-sector interventions with partners who are committed to safe medication use.

Potential partners in Safe Use include:

- Federal agencies
- Healthcare professionals and professional societies
- Pharmacies, hospitals, and other health care entities
- Patients, caregivers, consumers, and their representative organizations

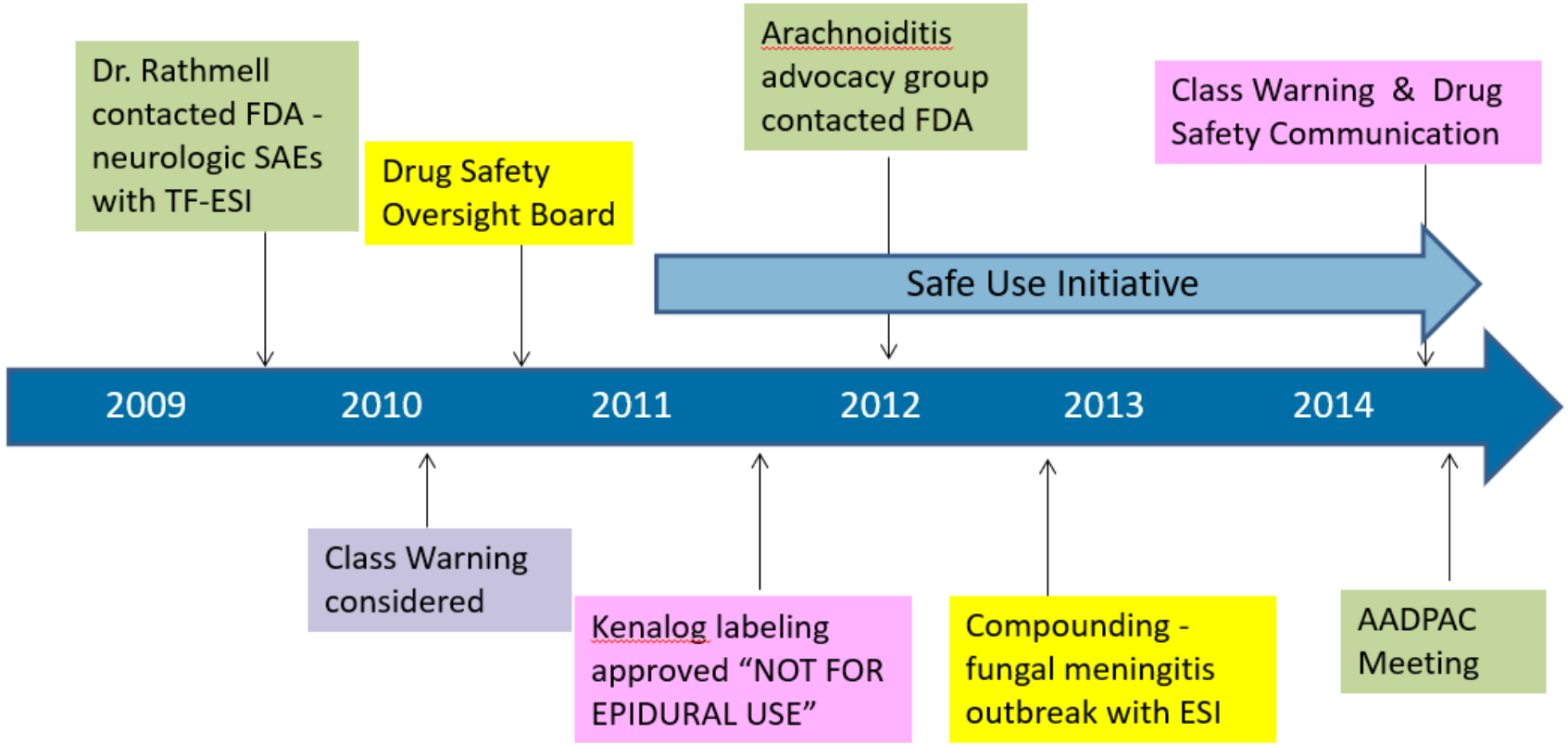
The Safe Use Initiative is one of three teams organizationally within Professional Affairs and Stakeholder Engagement, or "PASE."

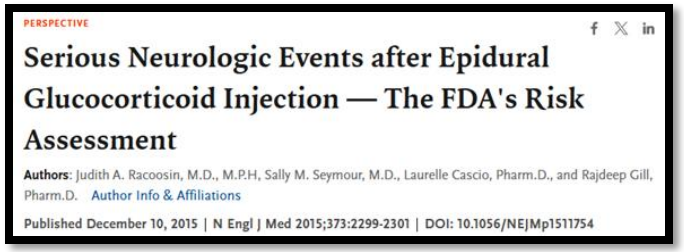
Through coordinated efforts, we can make significant improvements in the safe use of medications and reduce preventable harm from medication misuse, abuse, and errors.

Content current as of:
08/30/2022

Regulated Product(s)
Drugs

Regulatory History- neurological complications of epidural steroid injections (ESIs)*





PERSPECTIVE

Serious Neurologic Events after Epidural Glucocorticoid Injection — The FDA's Risk Assessment

Authors: Judith A. Racoosin, M.D., M.P.H, Sally M. Seymour, M.D., Laurelle Cascio, Pharm.D., and Rajdeep Gill, Pharm.D. Author Info & Affiliations

Published December 10, 2015 | N Engl J Med 2015;373:2299-2301 | DOI: 10.1056/NEJMp1511754

Dec 2015
"At times, the FDA must grapple with safety concerns related to off-label uses of FDA-approved medications."

SAEs: serious adverse reactions; TF-ESI: transforaminal epidural steroid injection; AADPAC: Anesthetic and Analgesic Drug Products Advisory Committee

Actionable output of the “Safe Use Initiative” project on the safety of epidural steroid injections

VIEWPOINT

Improving the Safety of Epidural Steroid Injections

Honorio T. Benzon, MD
Department of Anesthesiology, Northwestern University Feinberg School of Medicine, Chicago, Illinois.

Marc A. Huntoon, MD
Department of Anesthesiology, Vanderbilt University School of Medicine, Nashville, Tennessee.

James P. Rathmell, MD
Department of Anesthesiology, Massachusetts General Hospital and Harvard Medical School, Boston.

Epidural steroid injections are used to treat patients with low back or neck pain with a radicular component. Approximately 4800 epidural injections per 100 000 Medicare patients were performed in 2011, a total of 2.3 million procedures among Medicare patients alone.[1] This represents a substantial increase over the previous rate of 2100 per 100 000 Medicare beneficiaries in 2000.

The 2 approaches used to access the epidural space are (1) the interlaminar approach, in which the tip of the needle is placed in the posterior epidural space similar to epidural catheter placement in surgery and obstetrics, and (2) the transforaminal approach, in which the tip of the needle is placed in an intervertebral foramina where the spinal nerve exits the spinal canal. With the interlaminar approach, most of the injected drug remains in the posterior epidural space, whereas with the transforaminal approach, the drug is placed in close proximity to the (inflamed) spinal nerve and dorsal root ganglion and spreads into the lateral and anterior epidural space, the interspace between the spinal nerve and the herniated disk. Practitioners usually use the transforaminal approach when a single nerve root in one extremity is affected from a single lateral herniated disk and use the interlaminar approach when several spinal nerves are involved in one leg or in both legs, as in the case of central disk herniation.

Most physicians who perform epidural steroid injections use a particulate steroid (those commonly used include methylprednisolone acetate, triamcinolone acetonide, or betamethasone sodium phosphate/betamethasone sodium acetate) instead of a nonparticulate (dexamethasone sodium phosphate) because early studies suggested that the duration of pain relief was longer with the particulates. Recent studies, however, suggest the duration of relief to be comparable.[2]

from intravascular injection of the particulate steroid through 1 of the arteries (ascending or deep cervical artery or the radicular artery accompanying the spinal nerve) that communicates with the anterior spinal artery, resulting in a segmental cord infarct.[3,4] Injuries from nonparticulate steroids, such as dexamethasone, have been associated with temporary events such as blindness and lower extremity paralysis.[5,6] In addition, fungal meningitis has occurred from the injection of contaminated compounded methylprednisolone acetate.[7]

Suggestions to Improve the Safety of Epidural Steroid Injections

A multidisciplinary working group, consisting of specialists who had previously published research related to epidural steroid injections, discussed the adverse effects posed by the procedures and recommended safety improvements. Although the US Food and Drug Administration (FDA) Safe Use Initiative coordinated the working group's deliberations, it neither created nor influenced the final recommendations.

The recommendations of the working group were voted on by representatives of an initial list of several national organizations. The group's proposals were later discussed, revised, and voted on by representatives and boards of directors of an expanded group of national specialty organizations and medical societies, which included the following disciplines: anesthesiology, pain medicine, physical medicine and rehabilitation, neurosurgery, orthopedic surgery, and radiology. The recently published recommendations[8] included several important suggestions for improving the safety of epidural steroid injections (explanations, if needed, are in parentheses).

1. All cervical and lumbar interlaminar epidural steroid injections should be performed using image guid-

JAMA Published online March 30, 2015

Medicare study to estimate risk of serious spinal adverse events

Original research

Risk of serious spinal adverse events associated with epidural corticosteroid injections in the Medicare population

Efe Eworuke ,[1] Leah Crisafi,[2] Jiemin Liao,[3] Sandia Akhtar,[3] Martha Van Clief,[1] Judith A Racoosin,[1] Michael Wernecke,[3] Thomas E MaCurdy,[3] Jeffrey A Kelman,[4] David J Graham[1]

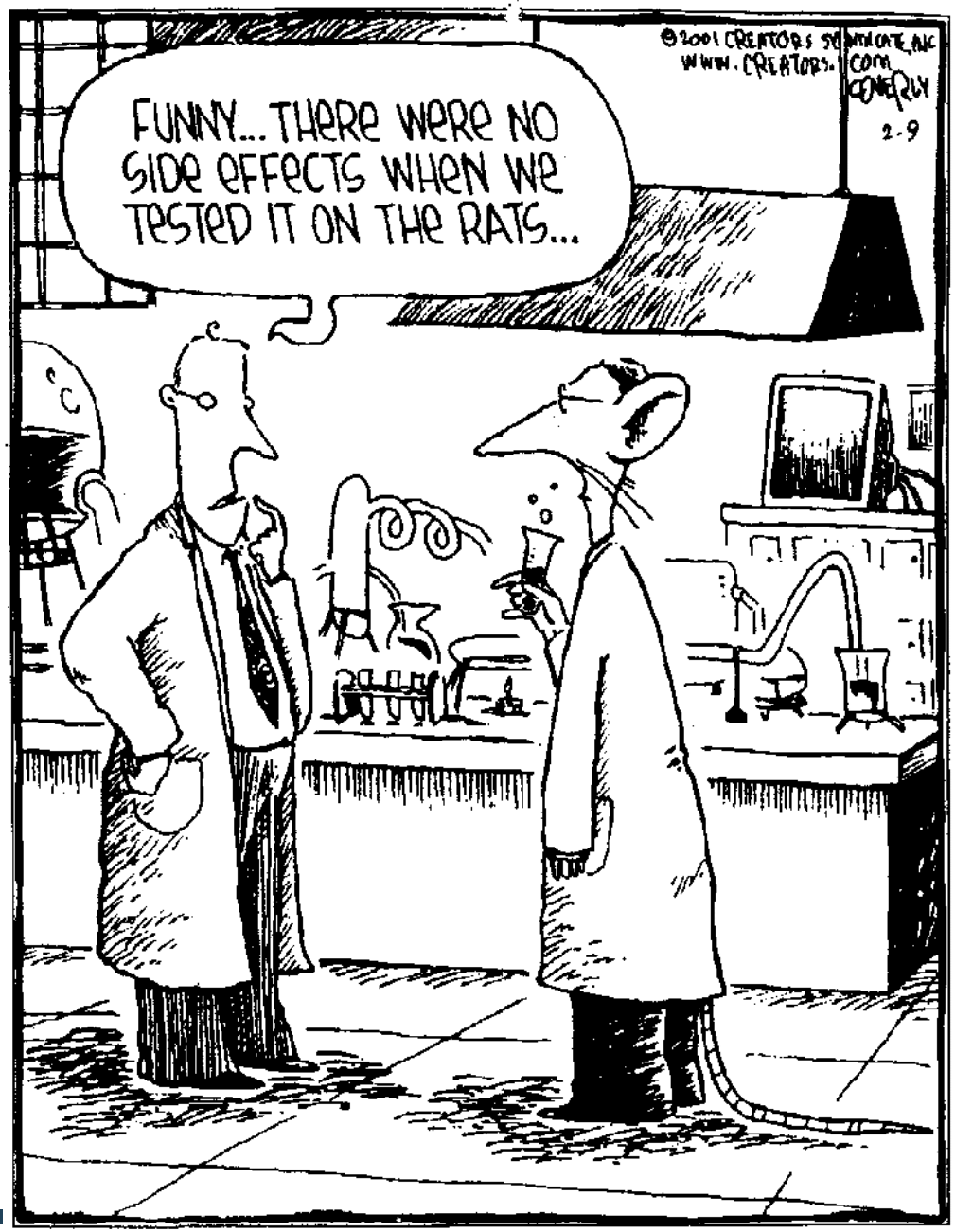
- Question… How often do these serious spinal adverse events happen?
- Characterize the rate of serious spinal adverse events (SSAEs) after ESI in the Medicare population
  - Compared the event rates by spinal cord level, injection approach and corticosteroid formulation.
  - Due to the common occurrence of stroke in the Medicare population, we restricted the study outcome to serious spinal events.

Eworuke E, Crisafi L, Liao J, et al. Reg Anesth Pain Med 2021;46:203–209.

Accumulated Wisdom

- Drug safety is a collaborative effort.
- We accomplish more with postmarket safety authorities.
- Data and analytic tools are essential.
- We can prevent some medication errors.
- We can warn about idiosyncratic side effects.
- We must protect our most vulnerable populations.
- We must communicate to stakeholders.
- Drug safety is important, but we must consider it in the context of benefit.

SPEED BUMP DAVE COVERLY



FDA's MedWatch Program

Outreach to Healthcare Professionals and their Patients
http://www.fda.gov/Safety/MedWatch/default.htm

- **1993** - MedWatch, The FDA Adverse Event Reporting Program announced by Commissioner David Kessler
  - Make it easier for providers to identify and report adverse events
  - make it clear what types of reports the FDA wants to receive
  - increase physician understanding and awareness of drug induced disease
  - more widely disseminate safety information on the FDA's actions that have resulted from adverse event and product problem reporting

- Delivering timely, science-based, clinically useful and actionable drug safety information to doctors and their patients for consideration at the point of shared decision-making for diagnostic and therapeutic decisions

Food and Drug Administration
MEDWATCH

From "Introducing MedWatch"; JAMA, 269(21), June 2, 1993

Designated Medical Events (DMEs)

- Designated Medical Events (DMEs) are serious adverse events that are generally rare and are often caused by exposure to drugs or a drug class.
- DMEs help focus attention on important advevents and prioritize pharmacovigilance activities (e.g., signal detection).
- The DME list does not have any regulatory significance.
- Identification of these events is a priority, even when the number of cases is small.
- DMEs are not intended to include events with a high prevalence in the general population.
- Examples: Stevens-Johnson Syndrome, torsades de pointes, hepatotoxicity

Postmarket safety example: Case reports/case series- Serious skin reactions

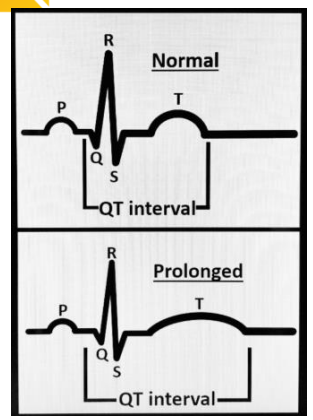
FDA Drug Safety Communication: FDA warns of rare but serious skin reactions with the pain reliever/fever reducer acetaminophen

Safety Announcement

[8-1-2013] The U.S. Food and Drug Administration (FDA) is informing the public that acetaminophen has been associated with a risk of rare but serious skin reactions. These skin reactions, known as Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), and acute generalized exanthematous pustulosis (AGEP), can be fatal. Acetaminophen is a common active ingredient to treat pain and reduce fever; it is included in many prescription and over-the-counter (OTC) products.

https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-warns-rare-serious-skin-reactions-pain-relieverfever-reducer#tabs-4
https://www.fda.gov/drugs/drug-safety-and-availability/fda-issues-agency-initiated-proposed-order-regarding-otc-monograph-drugs-containing-acetaminophen

QT prolongation/ Torsades de pointes (TdP)



JAMA 1990

Torsades de Pointes Occurring in Association With Terfenadine Use

Brian P. Monahan, MD; Clifford L. Ferguson, MD; Eugene S. Killeavy, MD; Bruce K. Lloyd, MD; James Troy; Louis R. Cantilena, Jr, MD, PhD

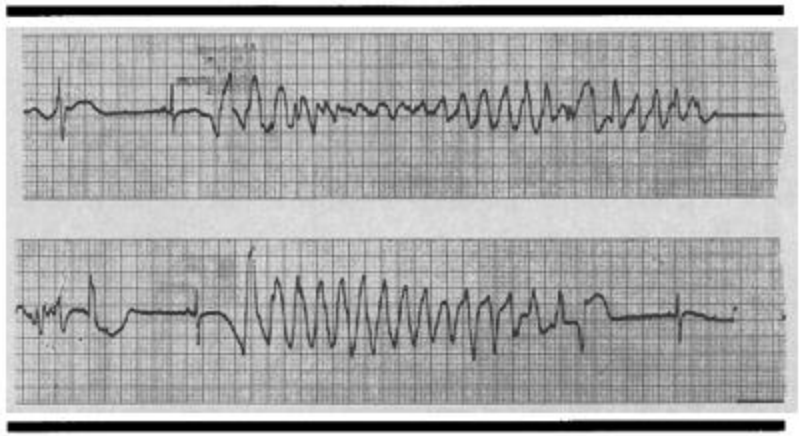


Fig 3.—Recordings of electrocardiographic monitor during near syncopal episode showing torsades de pointes rhythm abnormality.

- The life-threatening cardiac arrhythmia, TdP, emerged as a drug-induced safety issue with non-sedating antihistamines (e.g., terfenadine) when CYP3A4 inhibitors were taken concomitantly
- Observed with other non-cardiovascular drugs (e.g., methadone, antipsychotic drugs, antibiotics)
- TdP is related to prolongation of the QT interval representing delayed ventricular repolarization

"I've thrown in some prescription drugs that don't interact well."

New Yorker 10/28/2002

Timing of prescription drug withdrawals: 1975-2000

Table 2. Drugs Withdrawn From the Market for Safety Reasons, 1975-2000*

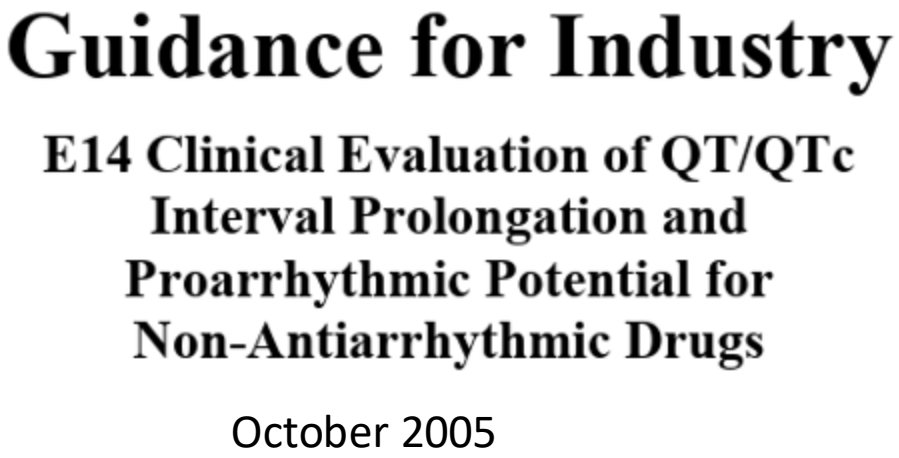
Drug Name	Food and Drug Administration Class	Drug Approval Date	Warning	Time to Withdrawal in Years	
Azaribine	Dermatologic (psoriasis)	January 1, 1975	Thromboembolism	2.4	
Ticrynafen	Antihypertensive	May 2, 1979	Hepatic toxicity	0.7	
Zomepirac sodium	Analgesic, nonsteroidal anti-inflammatory	October 28, 1980	Anaphylaxis	2.3	
Benoxaprofen	Analgesic, nonsteroidal anti-inflammatory	April 19, 1982	Jaundice	0.3	
Suprofen	Analgesic, nonsteroidal anti-inflammatory	December 24, 1984	Flank pain syndrome	1.3	
Nomifensine maleate	Antidepressant	December 31, 1984	Hemolytic anemia	1.4	
Terfenadine†	Antihistamine	May 8, 1985	Drug interactions causing cardiotoxicity	12.8	TdP
Encainide hydrochloride†	Antiarrhythmic	December 24, 1986	Increased mortality in patients with asymptomatic ventricular arrhythmias	5.0	
Astemizole†	Antihistamine	December 29, 1988	Drug interactions	10.5	TdP
Temafloxacin hydrochloride	Fluoroquinolone antibiotic	January 30, 1992	Hemolytic anemia	0.3	
			Hypoglycemia in elderly patients	0.3	
			Renal failure	0.3	
			Abnormal liver test results	0.3	
			Coagulopathy	0.3	
Flosequinan	Congestive heart failure	December 30, 1992	Increased mortality	0.5	
Cisapride†	Acid/peptic disorders	July 29, 1993	Drug interactions causing cardiotoxicity	6.6	TdP
Troglitazone†	Blood glucose regulator	January 29, 1997	Hepatic failure	3.1	
Mibefradil dihydrochloride	Antihypertensive calcium-channel blocker	June 20, 1997	Drug interactions	1.0	
Bromfenac sodium	Analgesic, nonsteroidal anti-inflammatory	July 15, 1997	Hepatic failure	1.0	
Grepafloxacin hydrochloride	Fluoroquinolone antibiotic	November 6, 1997	Cardiovascular events	2.0	TdP

*All drugs were approved between 1975 and 1999.
†Drug had a *Physicians' Desk Reference* black box warning prior to withdrawal.

Lasser et al. (Reprinted) JAMA, May 1, 2002—Vol 287, No. 17 2219

TdP= torsade de pointes

“Thorough QT study”


Guidance for Industry

E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs

October 2005

- “QT-IRT” - Interdisciplinary Review Team for QT Studies
  - MaPP 6020.14
  - Effective 10/16/2007
  - Provide expert review advice to sponsors and review divisions on TQT studies and to contribute to the evolution of the science by developing alternative methods for evaluating repolarization effects

Timing of prescription drug withdrawals: 1975-2000

Table 2. Drugs Withdrawn From the Market for Safety Reasons, 1975-2000*

Drug Name	Food and Drug Administration Class	Drug Approval Date	Warning	Time to Withdrawal in Years
Azaribine	Dermatologic (psoriasis)	January 1, 1975	Thromboembolism	2.4
Ticrynafen	Antihypertensive	May 2, 1979	Hepatic toxicity	0.7
Zomepirac sodium	Analgesic, nonsteroidal anti-inflammatory	October 28, 1980	Anaphylaxis	2.3
Benoxaprofen	Analgesic, nonsteroidal anti-inflammatory	April 19, 1982	Jaundice	0.3
Suprofen	Analgesic, nonsteroidal anti-inflammatory	December 24, 1984	Flank pain syndrome	1.3
Nomifensine maleate	Antidepressant	December 31, 1984	Hemolytic anemia	1.4
Terfenadine†	Antihistamine	May 8, 1985	Drug interactions causing cardiotoxicity	12.8
Encainide hydrochloride†	Antiarrhythmic	December 24, 1986	Increased mortality in patients with asymptomatic ventricular arrhythmias	5.0
Astemizole†	Antihistamine	December 29, 1988	Drug interactions	10.5
Temafloxacin hydrochloride	Fluoroquinolone antibiotic	January 30, 1992	Hemolytic anemia	0.3
			Hypoglycemia in elderly patients	0.3
			Renal failure	0.3
			Abnormal liver test results	0.3
			Coagulopathy	0.3
Flosequinan	Congestive heart failure	December 30, 1992	Increased mortality	0.5
Cisapride†	Acid/peptic disorders	July 29, 1993	Drug interactions causing cardiotoxicity	6.6
Troglitazone†	Blood glucose regulator	January 29, 1997	Hepatic failure	3.1
Mibefradil dihydrochloride	Antihypertensive calcium-channel blocker	June 20, 1997	Drug interactions	1.0
Bromfenac sodium	Analgesic, nonsteroidal anti-inflammatory	July 15, 1997	Hepatic failure	1.0
Grepafloxacin hydrochloride	Fluoroquinolone antibiotic	November 6, 1997	Cardiovascular events	2.0

*All drugs were approved between 1975 and 1999.
†Drug had a *Physicians' Desk Reference* black box warning prior to withdrawal.

Heptox

Heptox

Heptox

Heptox

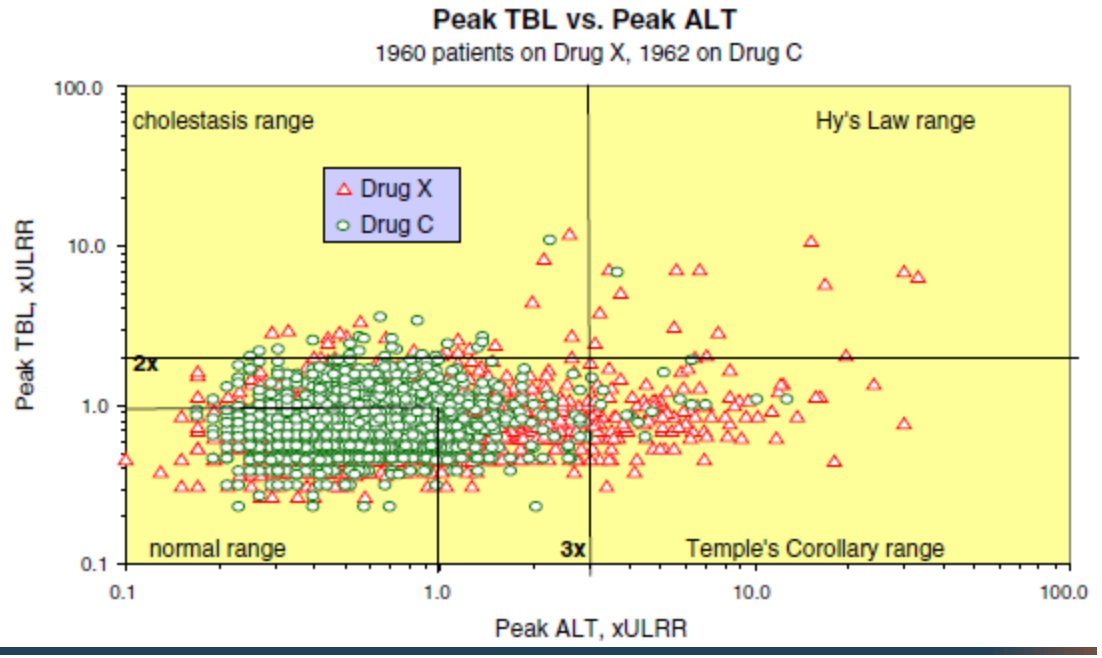
Heptox= hepatotoxicity/ drug-induced liver injury

Lasser et al.

Advances in detecting drug-induced liver injury

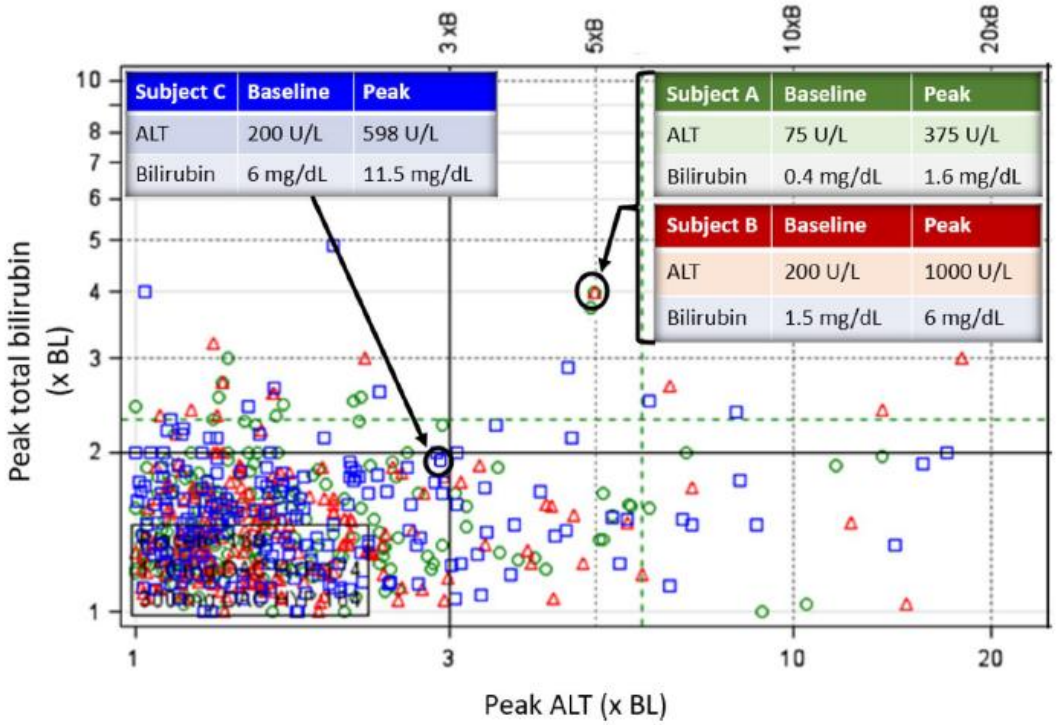
- 2009 Guidance for Industry- Drug-induced Liver Injury (DILI): Premarketing Clinical Evaluation
- Emphasized importance of assessing Hy's law cases

eDISH plot for patients with normal baseline liver tests^



^J Senior, Drug Safety 2014

eDISH plot for patients with abnormal baseline liver tests*



*J Amirzadegan et al, Drug Safety 2025

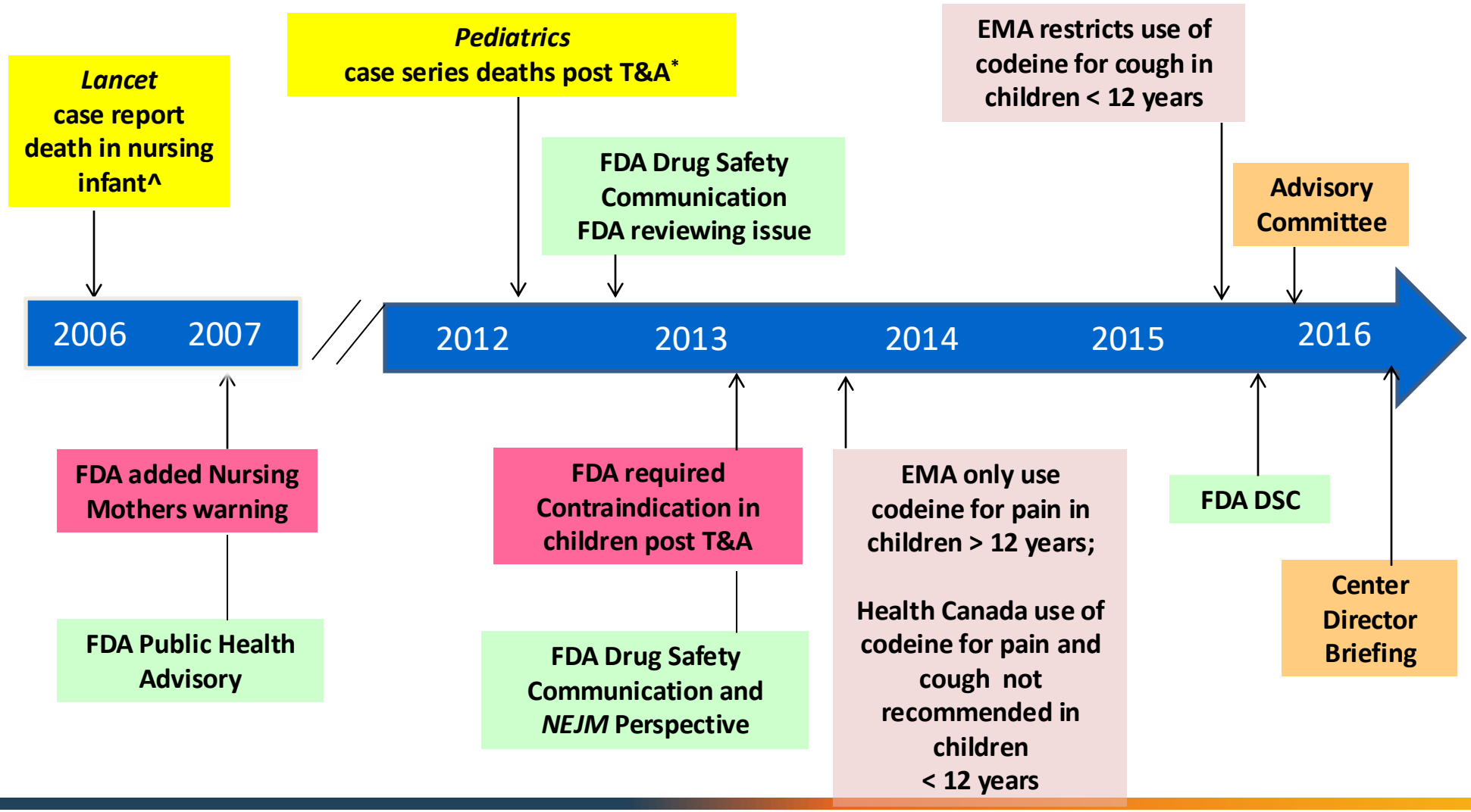
Accumulated Wisdom

- Drug safety is a collaborative effort.
- We accomplish more with postmarket safety authorities.
- Data and analytic tools are essential.
- We can prevent some medication errors.
- We can warn about idiosyncratic side effects.
- We must protect our most vulnerable populations.
- We must communicate to stakeholders.
- Drug safety is important, but we must consider it in the context of benefit.

Vulnerable populations

- Pediatrics
  - Risk of codeine polymorphic metabolism
- Geriatrics
  - Increased risk of stroke and death in patients with dementia-related psychosis
- Renal impairment
  - Aluminum toxicity with parenteral products
- Hepatic impairment
  - Obeticholic acid-associated hepatotoxicity

Relevant Regulatory History - Codeine



^Koren et al. Lancet 2006; 368:704 *Kelly et al. Pediatrics 2012; 129:1343-7 * T&A = tonsillectomy and adenoidectomy

Initial action- 2013 Boxed Warning and CI

The NEW ENGLAND JOURNAL of MEDICINE

Perspective

New Evidence about an Old Drug — Risk with Codeine after Adenotonsillectomy

Judith A. Racoosin, M.D., M.P.H., David W. Roberson, M.D., Michael A. Pacanowski, Pharm.D., M.P.H., and David R. Nielsen, M.D.

Subsequent action- April 2017: further restrictions on codeine; new restrictions on tramadol

- FDA's strongest warning, called a *Contraindication*, to the drug labels of codeine and tramadol alerting that codeine should not be used to treat pain or cough and tramadol should not be used to treat pain in children younger than 12 years.
- A new *Contraindication* to the tramadol label warning against its use in children younger than 18 years to treat pain after surgery to remove the tonsils and/or adenoids.
- A new *Warning* to the drug labels of codeine and tramadol to recommend against their use in adolescents between 12 and 18 years who are obese or have conditions such as obstructive sleep apnea or severe lung disease, which may increase the risk of serious breathing problems.
- A strengthened *Warning* to mothers that breastfeeding is not recommended when taking codeine or tramadol medicines due to the risk of serious adverse reactions in breastfed infants. These can include excess sleepiness, difficulty breastfeeding, or serious breathing problems that could result in death.

Accumulated Wisdom

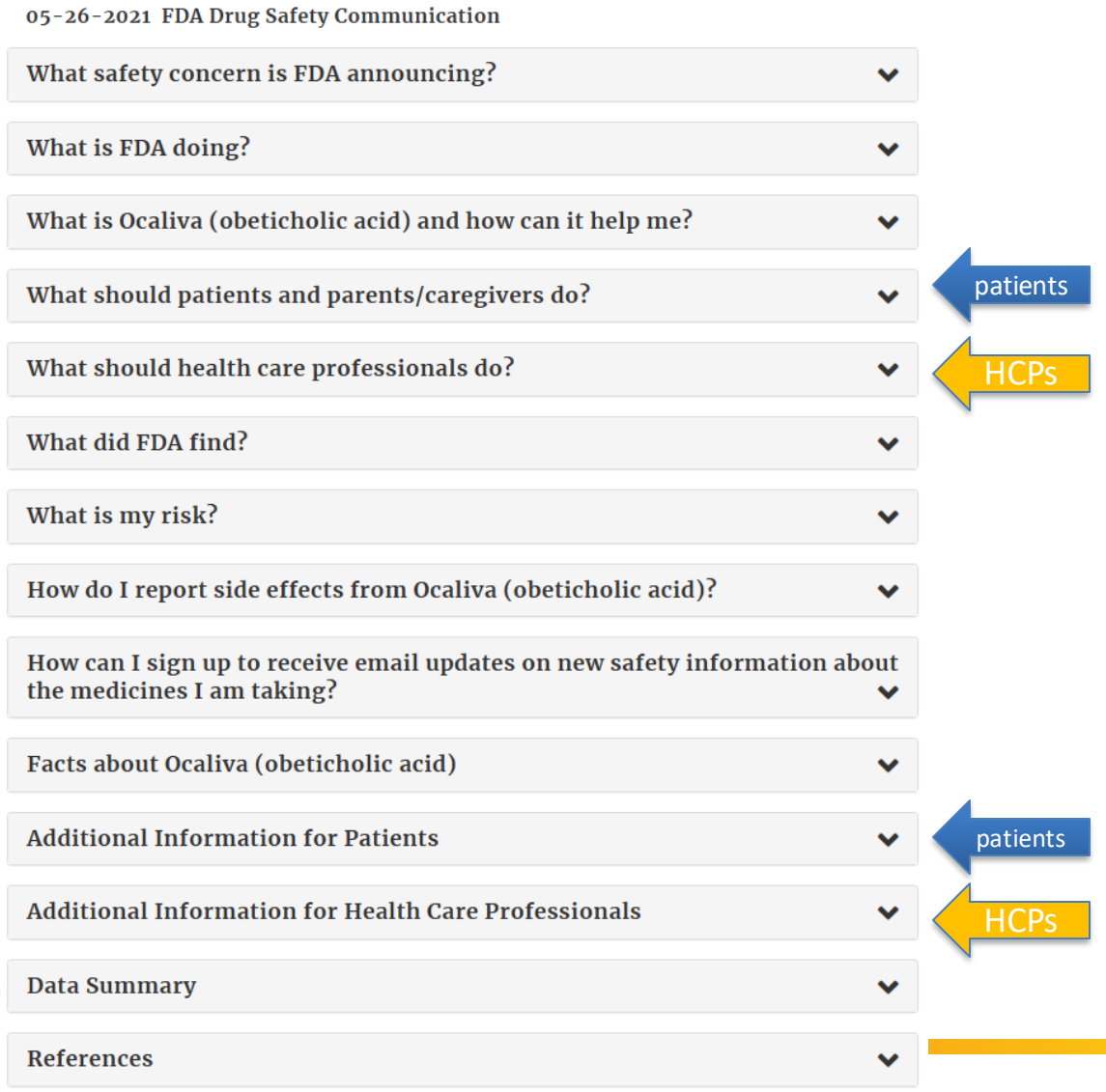
- Drug safety is a collaborative effort.
- We accomplish more with postmarket safety authorities.
- Data and analytic tools are essential.
- We can prevent some medication errors.
- We can warn about idiosyncratic side effects.
- We must protect our most vulnerable populations.
- We must communicate to stakeholders.
- Drug safety is important, but we must consider it in the context of benefit.

Risk Communication

- Safety Policy and Communication Staff established 2006 evolved into an Office of Communication
- Initially there were four formats for safety communications
  - Public Health Advisory
  - Information for Healthcare Professionals Sheet
  - Early Communication About an Ongoing Safety Review
  - Science Background Paper
- Distilled into a multiuser format- Drug Safety Communication

Drug Safety Communication example: restricting use of obeticholic acid in primary biliary cholangitis patients with decompensated cirrhosis and compensated cirrhosis with portal hypertension (5/26/2021)

- Drug Safety Communication format has evolved over the past 15 years
- Incorporates messaging to multiple audiences
  - Healthcare providers
  - Patients
  - Public

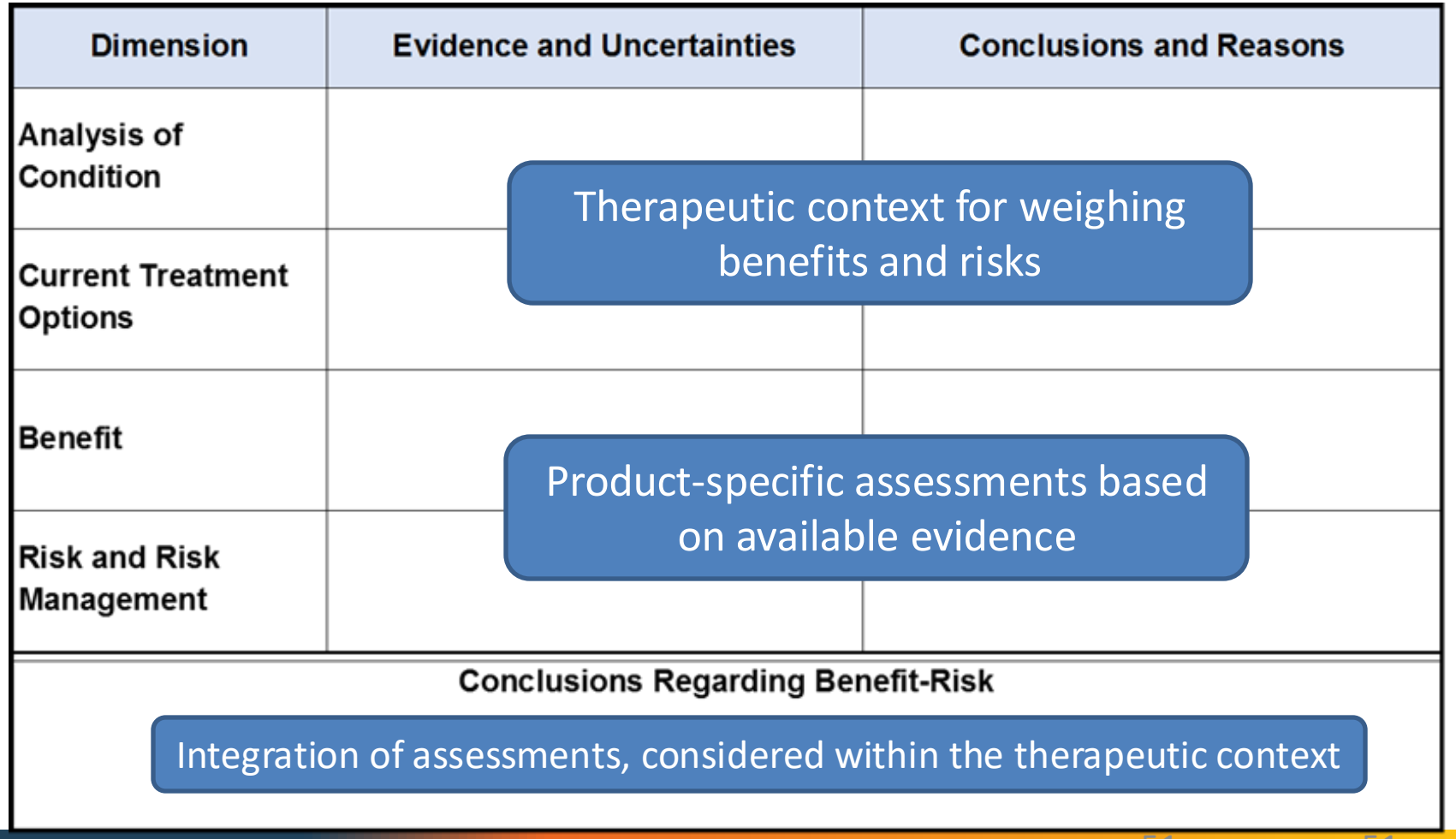


Accumulated Wisdom

- Drug safety is a collaborative effort.
- We accomplish more with postmarket safety authorities.
- Data and analytic tools are essential.
- We can prevent some medication errors.
- We can warn about idiosyncratic side effects.
- We must protect our most vulnerable populations.
- We must communicate to stakeholders.
- Drug safety is important, but we must consider it in the context of benefit.

The Benefit-Risk Framework is the vehicle for conducting FDA's benefit-risk assessment*

- It provides a structured, qualitative approach for identifying, assessing, and communicating important considerations that factor into a drug's benefit-risk assessment.
- Final guidance: Oct 2023
  https://www.fda.gov/regulatory-information/search-fda-guidance-documents/benefit-risk-assessment-new-drug-and-biological-products



*From 2022 slide set "Benefit-Risk Assessment Throughout the Drug Lifecycle", Decision Support and Analysis Staff, OPSA

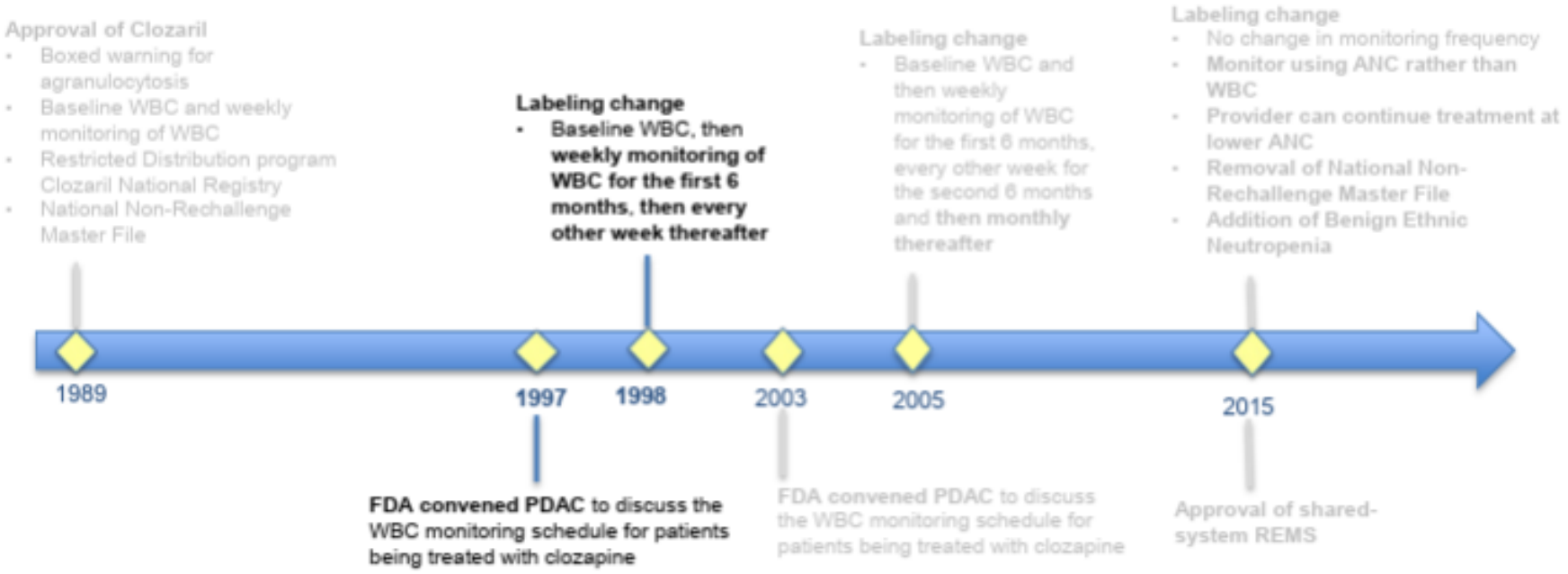
51

Clozapine

- Only medication approved for treatment-resistant schizophrenia (1989)
- Only medication approved for reducing suicidal behavior in patients with schizophrenia or schizoaffective disorder (2002)
- Substantial safety concerns
  - Agranulocytosis
    - Boxed warning
    - “no blood, no drug”
  - Seizures
  - Myocarditis

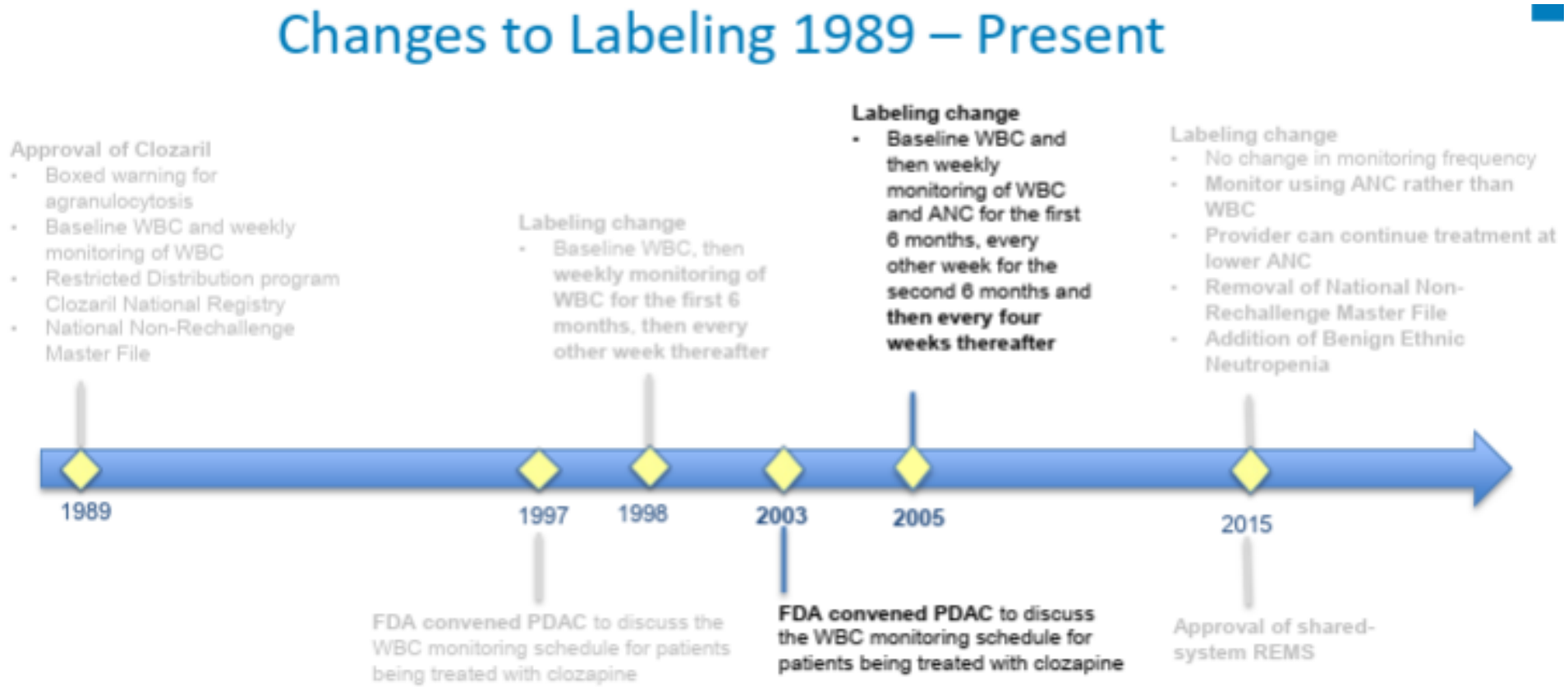
Clozapine Benefit/Risk Balance

Changes to Labeling 1989 – Present



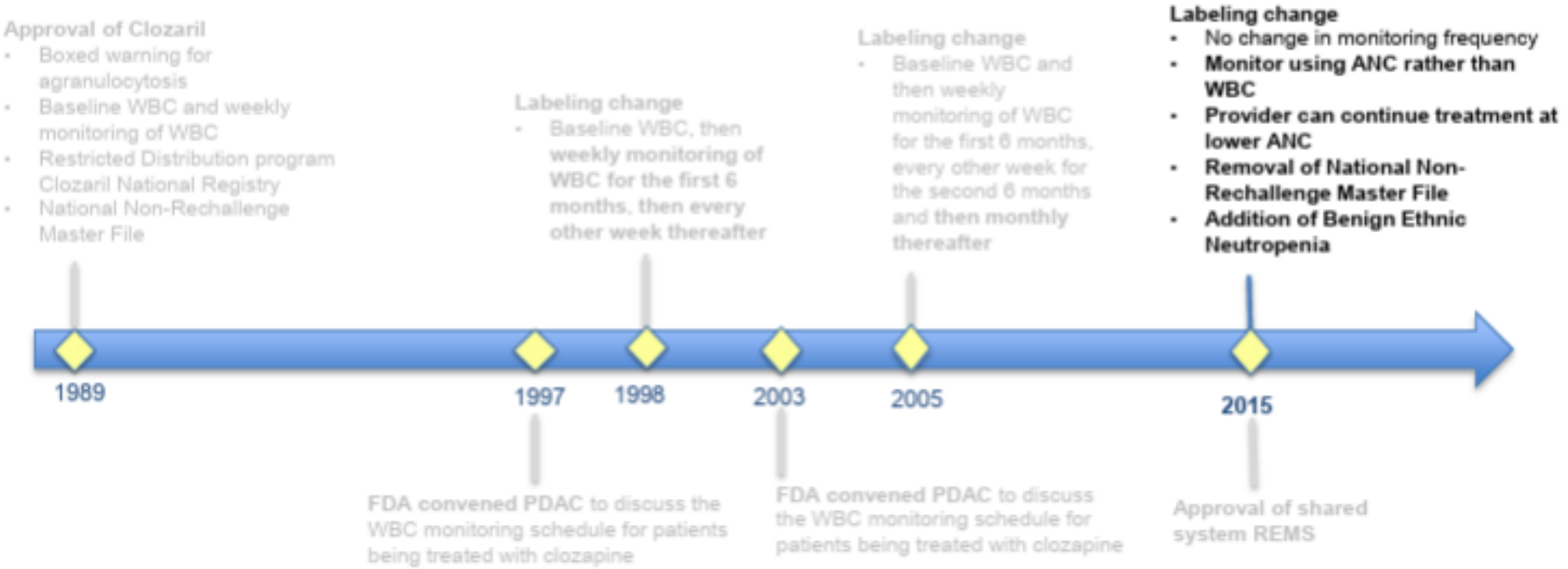
My first advisory committee presentation!

Clozapine Benefit/Risk Balance



Clozapine Benefit/Risk Balance

Changes to Labeling 1989 – Present



Clozapine Benefit/Risk Balance

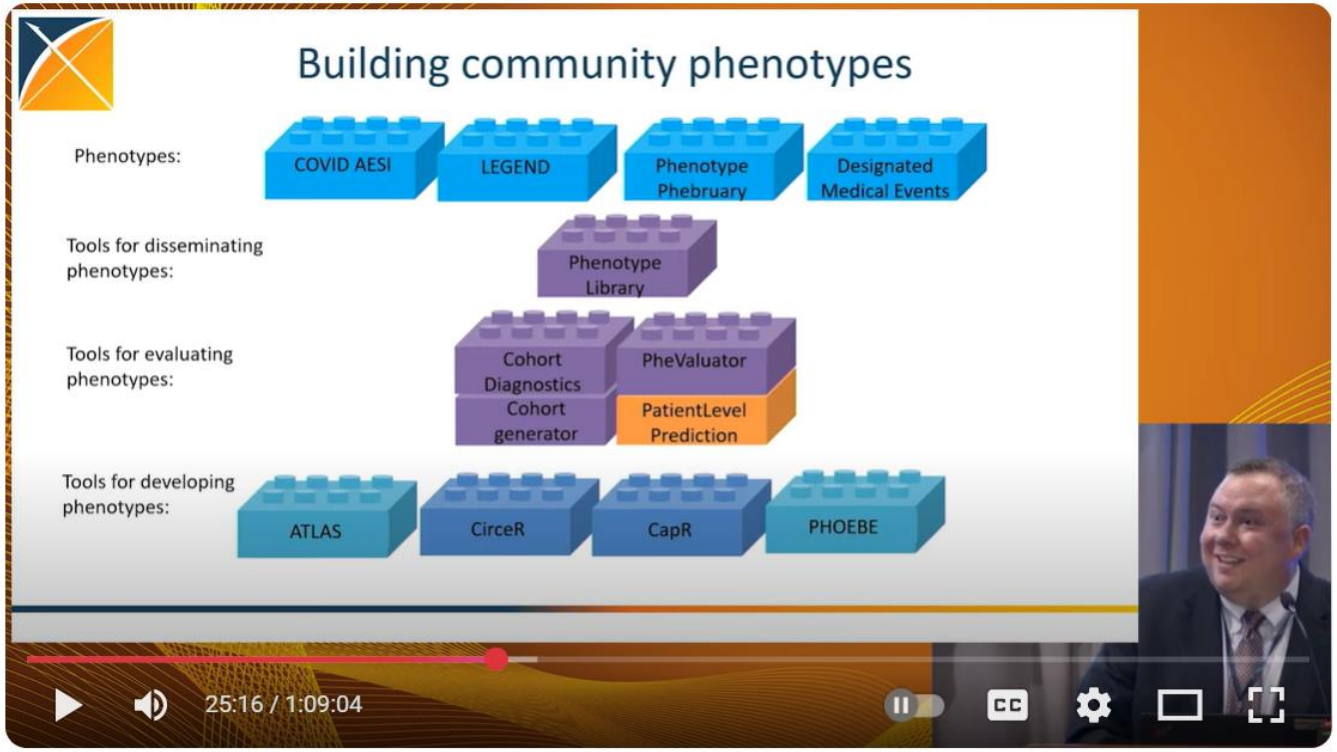
- Nov 2024 PDAC meeting – is the REMS still necessary?
  - Detailed review of the medical literature
  - Characterize whether practitioners are aware of the risk of severe neutropenia; Is absolute neutrophil count (ANC) monitoring being performed?
  - Multiple epidemiological studies to estimate the risk of neutropenia-related hospitalization and the risk of severe neutropenia

Clozapine Benefit/Risk Balance

- Nov 2024 PDAC meeting (continued)
  - Open public hearing: compelling testimony from family members and patients about the burden of the ANC monitoring, the hurdles to getting clozapine treatment, and the harmful consequences of not getting clozapine treatment
  - AC panel vote: REMS requirements create undue barriers to clozapine access without providing significant additional safety benefits, and they pointed to other medications with comparable risks that do not require such extensive REMS documentation.
- February 24, 2025: “FDA has determined that the REMS program for clozapine is no longer necessary to ensure the benefits of the medicine outweigh that risk. Eliminating the REMS is expected to decrease the burden on the health care delivery system and improve access to clozapine.”*

* https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/frequently-asked-questions-clozapine-rems-modification

Final thoughts…
Getting to “regulatory grade” evidence in medical product safety surveillance



(from Patrick’s OHDSI global symposium closing talk- 2022)

Gratitude/ Nothing at FDA gets done alone

Neuropharm safety team

- Jim Knudsen
- Mike Sevka
- Jerry Boehm
- Tarek Hammad
- Alice Hughes*
- Lisa Jones
- Marc Stone*
- Sally Yasuda*
- Lourdes Villalba
- Evelyn Mentari*

Sentinel Initiative

- Melissa Robb

Safety Regulatory Project Managers

- Katherine Won (DAAAP)
- Mark Liberatore* (DAAAP)
- Jessica Voqui (DAAAP)
- Thao Vu (DHN)

DAAAP Safety Team

- Dan Foster

Mentors

- Greg Burkhart
- Rusty Katz
- Paul Seligman

*Went on to become a Deputy Director for Safety

Contact info

- racoosin@ohdsi.org
- Nine People’s Favorite Thing mixcloud.com/ninepeoplesfave @ninepeoplesfave (Instagram)