OHDSI

OBSERVATIONAL HEALTH DATA SCIENCES AND INFORMATICS

Translation of Open-Source Analytics into Patient-Centered Care

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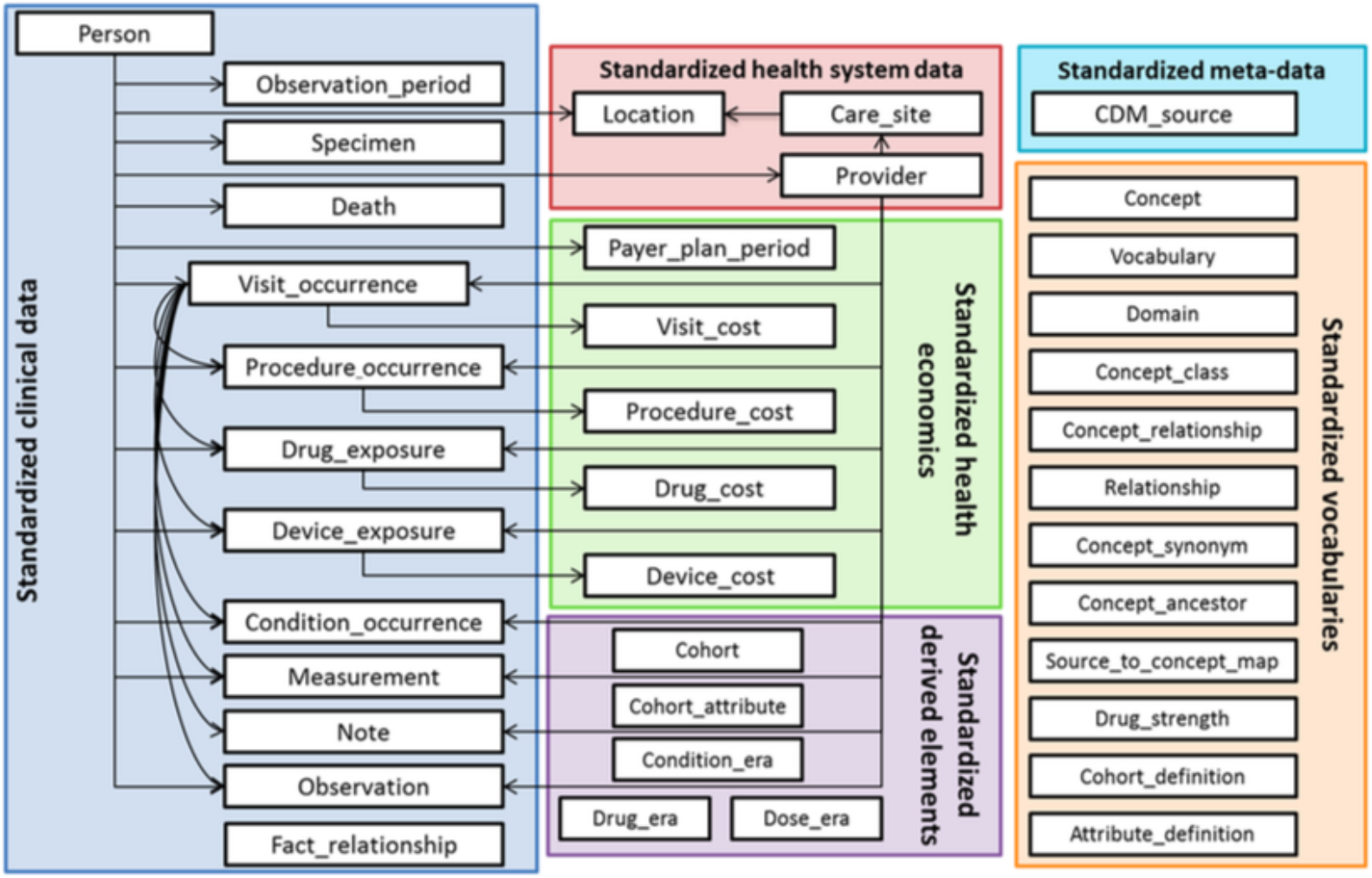
OHDSI Annual Symposium
October 20th, 2015

Funding Disclosures

- Funding from Bayer, Janssen, Lilly, Merck
  - Research
  - Consulting
  - Coming up with great drug names (Zaxyrbeard)

We've Arrived!

OMOP-IMEDS SYMPOSIUM 2013
HYATT REGENCY BETHESDA, ONE BETHESDA METRO CENTER, BETHESDA, MD 20814, USA
MEETING ROOM - HAVERFORD/BACCARAT
NOVEMBER 5 – 6, 2013


Standardized clinical data
Person
Observation_period
Specimen
Death
Visit_occurrence
Procedure_occurrence
Drug_exposure
Device_exposure
Condition_occurrence
Measurement
Note
Observation
Fact_relationship
Standardized health system data
Location
Care_site
Provider
Standardized health economics
Payer_plan_period
Visit_cost
Procedure_cost
Drug_cost
Device_cost
Standardized derived elements
Cohort
Cohort_attribute
Condition_era
Drug_era
Dose_era
Standardized meta-data
CDM_source
Standardized vocabularies
Concept
Vocabulary
Domain
Concept_class
Concept_relationship
Relationship
Concept_synonym
Concept_ancestor
Source_to_concept_map
Drug_strength
Cohort_definition
Attribute_definition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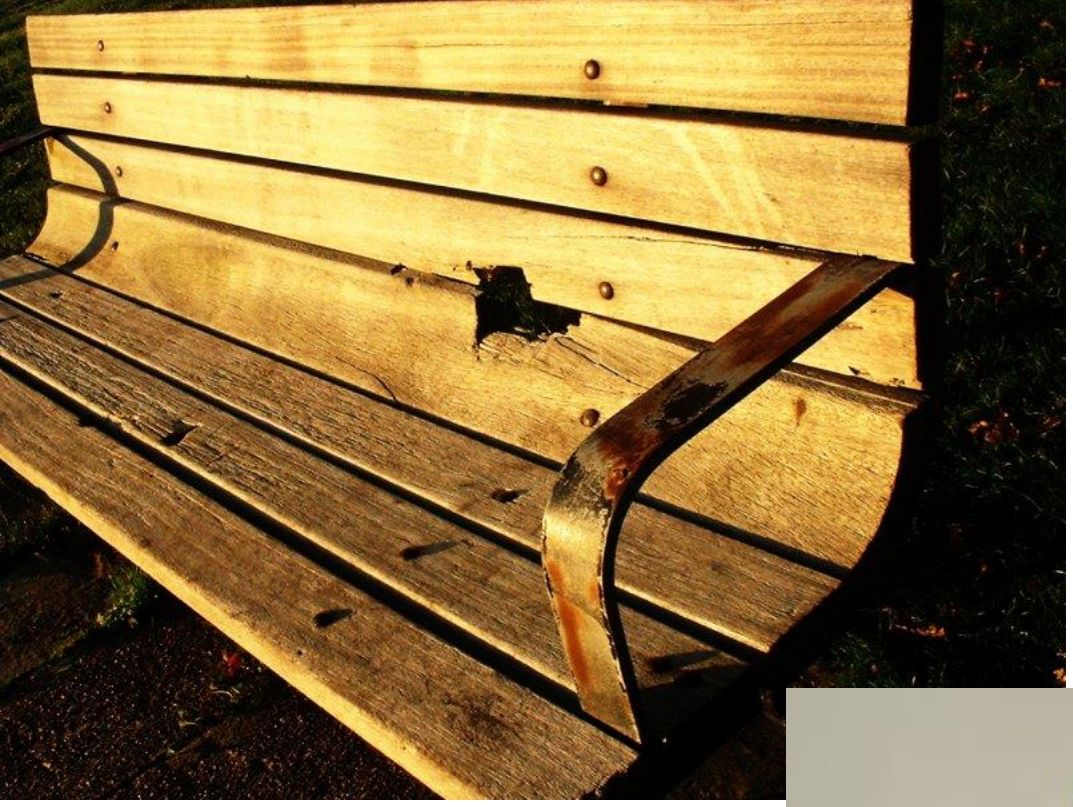
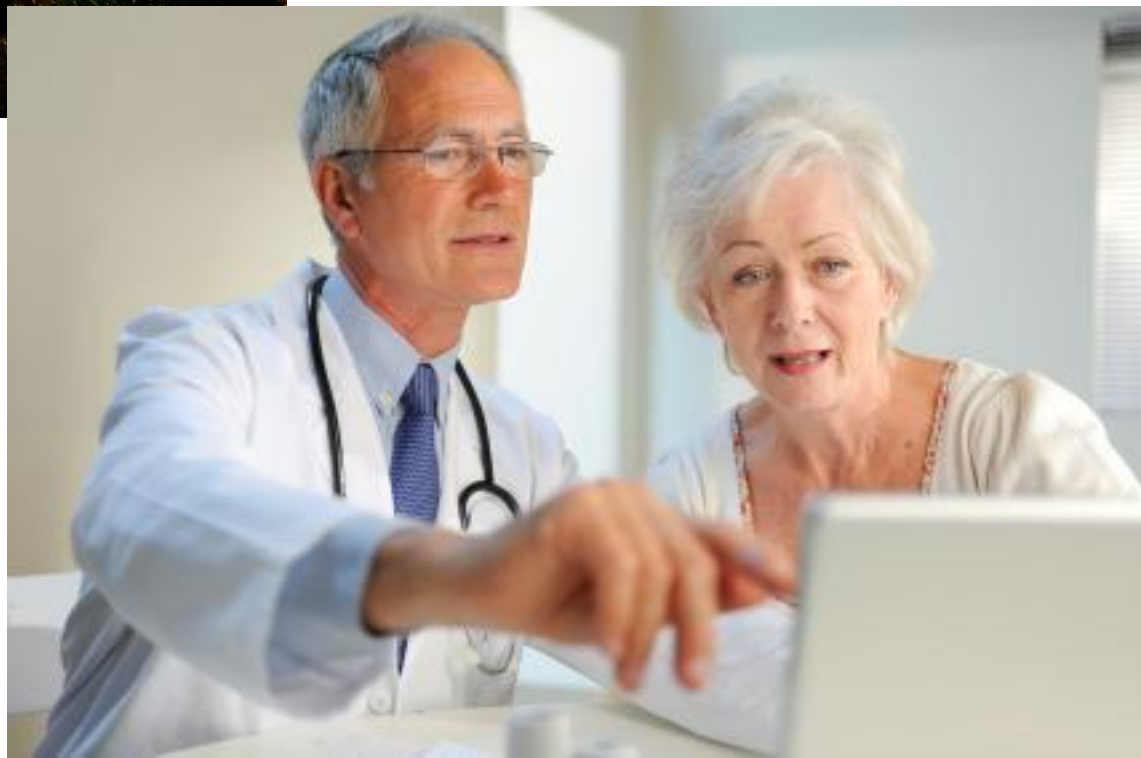
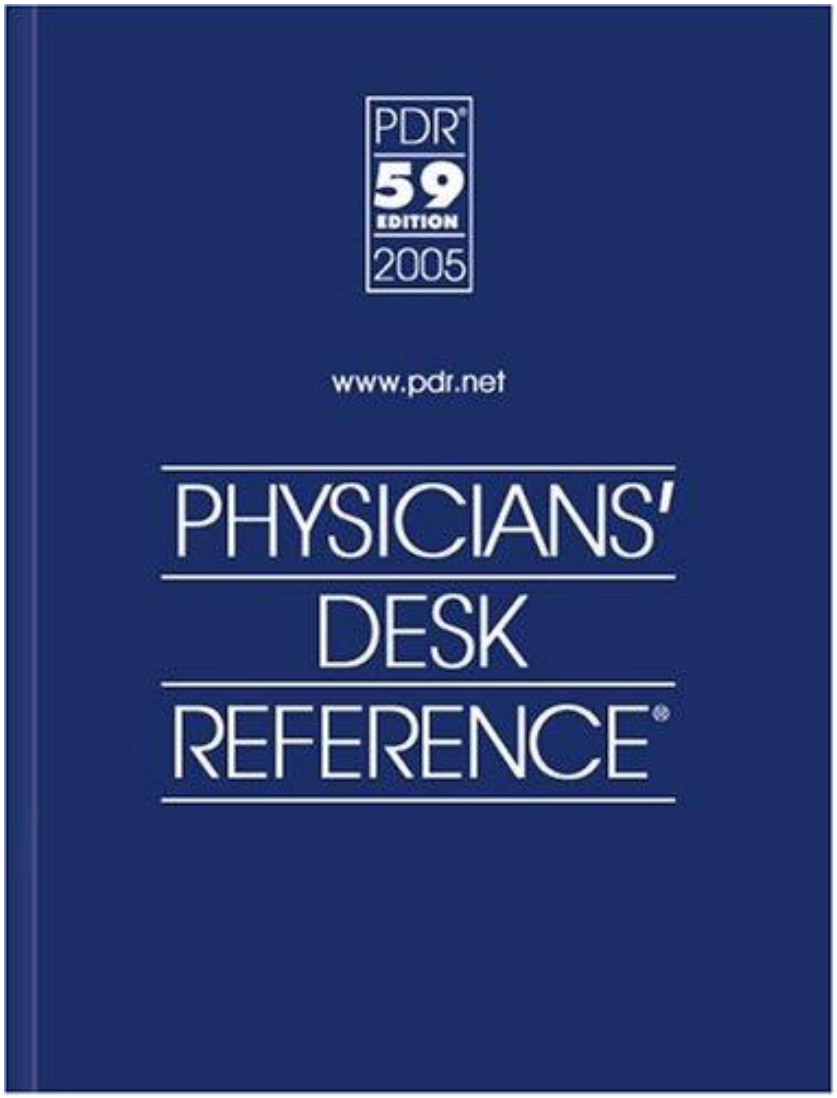




The ‘Bedside’ of Drug Safety Informatics

Communication of new and established drug safety evidence to improve patient care


PDR
59
EDITION
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DESK
REFERENCE

All NSAIDs, both COX-2 selective and non-selective, may have a similar risk. Patients with known CV disease or risk factors for CV disease may be at greater risk. To minimize the potential risk for an adverse CV event in patients treated with CELEBREX, the lowest effective dose should be used for the shortest duration consistent with individual patient treatment goals. Physicians and patients should remain alert for the development of such events, even in the absence of previous CV symptoms. Patients should be informed about the signs and/or symptoms of serious CV toxicity and the steps to take if they occur.

There is no consistent evidence that concurrent use of aspirin mitigates the increased risk of serious CV thrombotic events associated with NSAID use. The concurrent use of aspirin and CELEBREX does increase the risk of serious GI events [*see Warnings and Precautions (5.4)*].

Two large, controlled, clinical trials of a different COX-2 selective NSAID for the treatment of pain in the first 10-14 days following CABG surgery found an increased incidence of myocardial infarction and stroke [*see Contraindications (4)*].

.2 Hypertension

As with all NSAIDs, CELEBREX can lead to the onset of new hypertension or worsening of preexisting hypertension, either of which may contribute to the increased incidence of CV events. Patients taking thiazides or loop diuretics may have impaired response to these therapies when taking NSAIDs. NSAIDs, including CELEBREX, should be used with caution in patients with hypertension. Blood pressure should be monitored closely during the initiation of therapy with CELEBREX and throughout the course of therapy. The rates of hypertension from the CLASS trial in the CELEBREX, ibuprofen and diclofenac-treated patients were 2.4%, 4.2% and 2.5%, respectively [*see Clinical Studies (14.6)*].

.3 Congestive Heart Failure and Edema

Fluid retention and edema have been observed in some patients taking NSAIDs, including CELEBREX [*see Adverse Reactions (6.1)*]. In the CLASS study [*see Clinical Studies (14.6)*], the Kaplan-Meier cumulative rates at 9 months of peripheral edema in patients on CELEBREX 400 mg twice daily (4-fold and 2-fold the recommended OA and RA doses, respectively), ibuprofen 800 mg three times daily and diclofenac 75 mg twice daily were 4.5%, 6.9% and 4.7%, respectively. CELEBREX should be used with caution in patients with fluid retention or heart failure.

.4 Gastrointestinal (GI) Effects
Risk of GI Ulceration, Bleeding, and Perforation

NSAIDs, including CELEBREX, can cause serious gastrointestinal events including bleeding, ulceration, and perforation of the stomach, small intestine or large intestine, which can be fatal. These serious adverse events can occur at any time, with or without warning symptoms, in patients treated with NSAIDs. Only one in five patients who develop a serious upper GI adverse event on NSAID therapy is symptomatic. Complicated and symptomatic ulcer rates were 0.78% at nine months for all patients in the CLASS trial, and 2.19% for the subgroup on low-dose ASA. Patients 65 years of age and older had an incidence of 1.40% at nine months, 3.06% when also taking ASA [*see Clinical Studies (14.6)*]. With longer duration of use of NSAIDs, there is a trend for increasing the likelihood of developing a serious GI event at some time during the course of therapy. However, even short-term therapy is not without risk.

NSAIDs should be prescribed with extreme caution in patients with a prior history of ulcer disease or gastrointestinal bleeding. Patients with a prior history of peptic ulcer disease and/or gastrointestinal bleeding who use NSAIDs have a greater than 10-fold increased risk for developing a GI bleed compared to patients with neither of these risk factors. Other factors that increase the risk of GI bleeding in patients treated with NSAIDs include concomitant use of oral corticosteroids or anticoagulants, longer duration of NSAID therapy, smoking, use of alcohol, older age, and poor general health status. Most spontaneous reports of fatal GI events are in elderly or debilitated patients and therefore special care should be taken in treating this population.

To minimize the potential risk for an adverse GI event, the lowest effective dose should be used for the shortest duration consistent with individual patient treatment goals. Physicians and patients should remain alert for signs and symptoms of GI ulceration and bleeding during CELEBREX therapy and promptly initiate additional evaluation and treatment if a serious GI adverse event is suspected. For high-risk patients, alternate therapies that do not involve NSAIDs should be considered.

5.5 Hepatic Effects

Borderline elevations of one or more liver-associated enzymes may occur in up to 15% of patients taking NSAIDs, and notable elevations of ALT or AST (approximately 3 or more times the upper limit of normal) have been reported in approximately 1% of patients in clinical trials with NSAIDs. These laboratory abnormalities may progress, may remain unchanged, or may be transient with continuing therapy. Rare cases of severe hepatic reactions, including jaundice and fatal fulminant hepatitis, liver necrosis and hepatic failure (some with fatal outcome) have been reported with NSAIDs, including CELEBREX [*see Adverse Reactions (6.1)*]. In controlled clinical trials of CELEBREX, the incidence of borderline elevations (greater than or equal to 1.2 times and less than 3 times the upper limit of normal) of liver associated enzymes was 6% for CELEBREX and 5% for placebo, and approximately 0.2% of patients taking CELEBREX and 0.3% of patients taking placebo had notable elevations of ALT and AST.

A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be monitored carefully for evidence of the development of a more severe hepatic reaction while on therapy with CELEBREX. If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), CELEBREX should be discontinued.

5.6 Renal Effects

Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury. Renal toxicity has als been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of an NSAID may cause a dose-dependent reduction in prostaglandin formation and, secondari in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunctic those taking diuretics, ACE-inhibitors, angiotensin II receptor antagonists, and the elderly. Discontinuation of NSAID therapy usually followed by recovery to the pretreatment state. Clinical trials with CELEBREX have shown renal effects similar to those observed with comparator NSAIDs.

No information is available from controlled clinical studies regarding the use of CELEBREX in patients with advanced renal disease. Therefore, treatment with CELEBREX is not recommended in these patients with advanced renal disease. If CELEBREX therapy must be initiated, close monitoring of the patient's renal function is advisable.

5.7 Anaphylactoid Reactions

As with NSAIDs in general, anaphylactoid reactions have occurred in patients without known prior exposure to CELEBREX. In post-marketing experience, rare cases of anaphylactic reactions and angioedema have been reported in patients receiving CELEBREX. CELEBREX should not be given to patients with the aspirin triad. This symptom complex typically occurs in asthmatic patients who experience rhinitis with or without nasal polyps, or who exhibit severe, potentially fatal bronchospasm after taking aspirin or other NSAIDs [*see Contraindications (4), Warnings and Precautions (5.7)*]. Emergency help should be sought in cases where an anaphylactoid reaction occurs.

5.8 Skin Reactions

CELEBREX is a sulfonamide and can cause serious skin adverse events such as exfoliative dermatitis, Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. These serious events can occur without warning and in patients without prior known sulfa allergy. Patients should be informed about the signs and symptoms of serious skin manifestations and use of the drug should be discontinued at the first appearance of skin rash or any other sign of hypersensitivity.

5.9 Pregnancy

In late pregnancy, starting at 30 weeks gestation, CELEBREX should be avoided because it may cause premature closure of the ductus arteriosus [*see Use in Specific Populations (8.1)*].

5.10 Corticosteroid Treatment

CELEBREX cannot be expected to substitute for corticosteroids or to treat corticosteroid insufficiency. Abrupt discontinuation of corticosteroids may lead to exacerbation of corticosteroid-responsive illness. Patients on prolonged corticosteroid therapy should have their therapy tapered slowly if a decision is made to discontinue corticosteroids.

5.11 Hematological Effects

Anemia is sometimes seen in patients receiving CELEBREX. In controlled clinical trials the incidence of anemia was 0.6% with CELEBREX and 0.4% with placebo. Patients on long-term treatment with CELEBREX should have their hemoglobin or hematocrit checked if they exhibit any signs or symptoms of anemia or blood loss. CELEBREX does not generally affect platelet counts, prothrombin time (PT), or partial thromboplastin time (PTT), and does not inhibit platelet aggregation at indicated dosages [*see Clinical Pharmacology (12.2)*].

5.12 Disseminated Intravascular Coagulation (DIC)

CELEBREX should be used only with caution in pediatric patients with systemic onset JRA due to the risk of disseminated intravascular coagulation.

5.13 Preexisting Asthma

Patients with asthma may have aspirin-sensitive asthma. The use of aspirin in patients with aspirin-sensitive asthma has been associated with severe bronchospasm, which can be fatal. Since cross reactivity, including bronchospasm, between aspirin and other nonsteroidal anti-inflammatory drugs has been reported in such aspirin-sensitive patients, CELEBREX should not be administered to patients with this form of aspirin sensitivity and should be used with caution in patients with preexisting asthma.

5.14 Laboratory Tests

Because serious GI tract ulcerations and bleeding can occur without warning symptoms, physicians should monitor for signs or symptoms of GI bleeding. Patients on long-term treatment with NSAIDs should have a CBC and a chemistry profile checked periodically. If abnormal liver tests or renal tests persist or worsen, CELEBREX should be discontinued.

In controlled clinical trials, elevated BUN occurred more frequently in patients receiving CELEBREX compared with patients on placebo. This laboratory abnormality was also seen in patients who received comparator NSAIDs in these studies. The clinical significance of this abnormality has not been established.

5.15 Inflammation

The pharmacological activity of CELEBREX in reducing inflammation, and possibly fever, may diminish the utility of these diagnostic signs in detecting infectious complications of presumed noninfectious, painful conditions.

5.16 Concomitant NSAID Use

The concomitant use of CELEBREX with any dose of a non-aspirin NSAID should be avoided due to the potential for increased risk of adverse reactions.

6. ADVERSE REACTIONS

Of the CELEBREX-treated patients in the pre-marketing controlled clinical trials, approximately 4,250 were patients with OA, approximately 2,100 were patients with RA, and approximately 1,050 were patients with post-surgical pain. More than 8,500 patients received a total daily dose of CELEBREX of 200 mg (100 mg twice daily or 200 mg once daily) or more, including more than 400 treated at 800 mg (400 mg twice daily). Approximately 3,900 patients received CELEBREX at these doses for 6 months or more; approximately 2,300 of these have received it for 1 year or more and 124 of these have received it for 2 years or more.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

6.1 Pre-marketing Controlled Arthritis Trials

Table 1 lists all adverse events, regardless of causality, occurring in ≥2% of patients receiving CELEBREX from 12 controlled studies conducted in patients with OA or RA that included a placebo and/or a positive control group. Since these 12 trials were of different durations, and patients in the trials may not have been exposed for the same duration of time, these percentages do not capture cumulative rates of occurrence.

Table 1: Adverse Events Occurring in ≥2% of CELEBREX Patients from Pre-marketing Controlled Arthritis Trials

	CBX N=4146	Placebo N=1864	NAP N=1366	DCF N=387	IBU N=345
Gastrointestinal					
Abdominal Pain	4.1%	2.8%	7.7%	9.0%	9.0%
Diarrhea	5.6%	3.8%	5.3%	9.3%	5.8%
Dyspepsia	8.8%	6.2%	12.2%	10.9%	12.8%
Flatulence	2.2%	1.0%	3.6%	4.1%	3.5%
Nausea	3.5%	4.2%	6.0%	3.4%	6.7%
Body as a whole					
Back Pain	2.8%	3.6%	2.2%	2.6%	0.9%
Peripheral Edema	2.1%	1.1%	2.1%	1.0%	3.5%
Injury-Accidental	2.9%	2.3%	3.0%	2.6%	3.2%
Central, Peripheral Nervous system					
Dizziness	2.0%	1.7%	2.6%	1.3%	2.3%
Headache	15.8%	20.2%	14.5%	15.5%	15.4%
Psychiatric					
Insomnia	2.3%	2.3%	2.9%	1.3%	1.4%
Respiratory					
Pharyngitis					
Rhinitis	2.3%	1.1%	1.7%	1.6%	2.6%
Sinusitis	2.0%	1.3%	2.4%	2.3%	0.6%
Upper Respiratory Infection	5.0% 8.1%	4.3% 6.7%	4.0% 9.9%	5.4% 9.8%	5.8% 9.9%
Skin					
Rash	2.2%	2.1%	2.1%	1.3%	1.2%

CBX = CELEBREX 100 – 200 mg twice daily or 200 mg once daily;
NAP = Naproxen 500 mg twice daily;
DCF = Diclofenac 75 mg twice daily;
IBU = Ibuprofen 800 mg three times daily.

LABEL: CELEBREX- celecoxib capsule

LABEL RSS SHARE

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DailyMed is no longer displaying pill images from RxImage. For more information, click here.

SAFETY

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- Clinical Trials
- + PubMed
- Biochemical Data Summary

MORE INFO FOR THIS DRUG

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- RxNorm
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NDC Code(s): 0025-1515-01, 0025-1520-31, 0025-1520-34, 0025-1520-51, view more
Packager: G.D. Searle LLC Division of Pfizer Inc

Category: HUMAN PRESCRIPTION DRUG LABEL
DEA Schedule: None
Marketing Status: New Drug Application

DRUG LABEL INFORMATION

Updated 06/15

If you are a consumer or patient please visit this version.

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VIEW ALL SECTIONS

BOXED WARNING (WHAT IS THIS?)

Cardiovascular Risk - CELEBREX may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. All nonsteroidal ...

WARNING: CARDIOVASCULAR AND GASTROINTESTINAL RISKS

Cardiovascular Risk

- CELEBREX may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. All nonsteroidal anti-inflammatory drugs (NSAIDs) may have a similar risk. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk. *(5.1,14.6)*
- CELEBREX is contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery. *(4, 5.1)*

Gastrointestinal Risk

- NSAIDs, including CELEBREX, cause an increased risk of serious gastrointestinal adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious gastrointestinal events. *(5.4)*

CLOSE

Gastrointestinal:	Constipation, diverticulitis, dysphagia, eructation, esophagitis, gastritis, gastroenteritis, gastroesophageal reflux, hemorrhoids, hiatal hernia, melena, dry mouth, stomatitis, tenesmus, vomiting
Cardiovascular:	Aggravated hypertension, angina pectoris, coronary artery disorder, myocardial infarction
General:	Allergy aggravated, allergic reaction, chest pain, cyst NOS, edema generalized, face edema, fatigue, fever, hot flushes, influenza-like symptoms, pain, peripheral pain
Central, peripheral nervous system:	Leg cramps, hypertonia, hypoesthesia, migraine, paresthesia, vertigo
Hearing and vestibular:	Deafness, tinnitus
Heart rate and rhythm:	Palpitation, tachycardia
Liver and biliary:	Hepatic function abnormal, SGOT increased, SGPT increased
Metabolic and nutritional:	BUN increased, CPK increased, hypercholesterolemia, hyperglycemia, hypokalemia, NPN increased, creatinine increased, alkaline phosphatase increased, weight increased
Musculoskeletal:	Arthralgia, arthrosis, myalgia, synovitis, tendinitis
Platelets (bleeding or clotting):	Ecchymosis, epistaxis, thrombocythemia
Psychiatric:	Anorexia, anxiety, appetite increased, depression, nervousness, somnolence
Hemic:	Anemia
Respiratory:	Bronchitis, bronchospasm, bronchospasm aggravated, coughing, dyspnea, laryngitis, pneumonia
Skin and appendages:	Alopecia, dermatitis, photosensitivity reaction, pruritus, rash erythematous, rash maculopapular, skin disorder, skin dry, sweating increased, urticaria
Application site disorders:	Cellulitis, dermatitis contact
Urinary:	Albuminuria, cystitis, dysuria, hematuria, micturition frequency, renal calculus

ARCHIVES OF
INTERNAL MEDICINE

Arch Intern Med. 2011 May 23;171(10):944-6.

A quantitative analysis of adverse events and "overwarning" in drug labeling.

Duke J, Friedlin J, Ryan P.

Regenstrief Institute, Indiana University School of Medicine, Indianapolis, USA. jduke@regenstrief.org

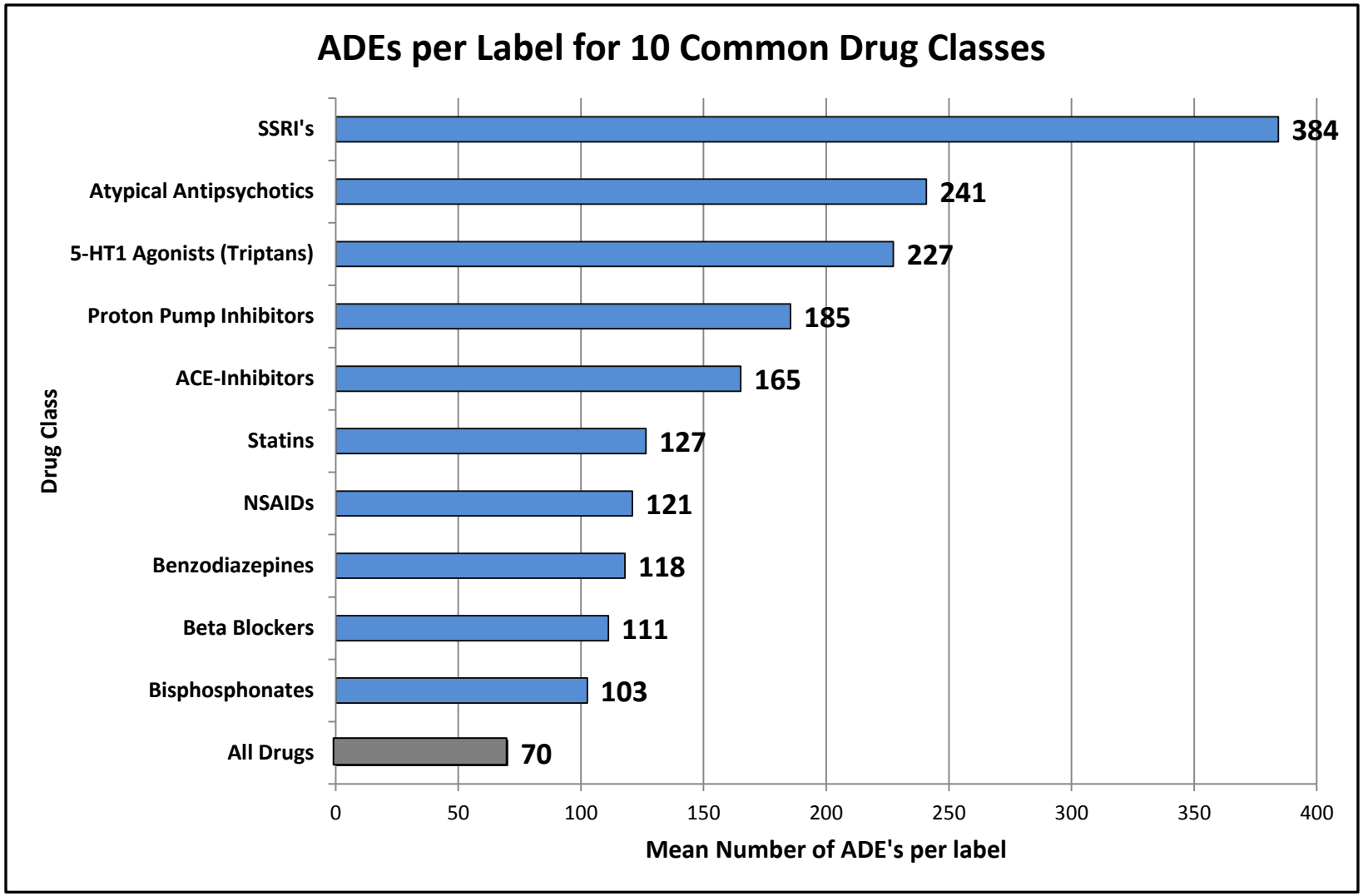
Common Things Being Common

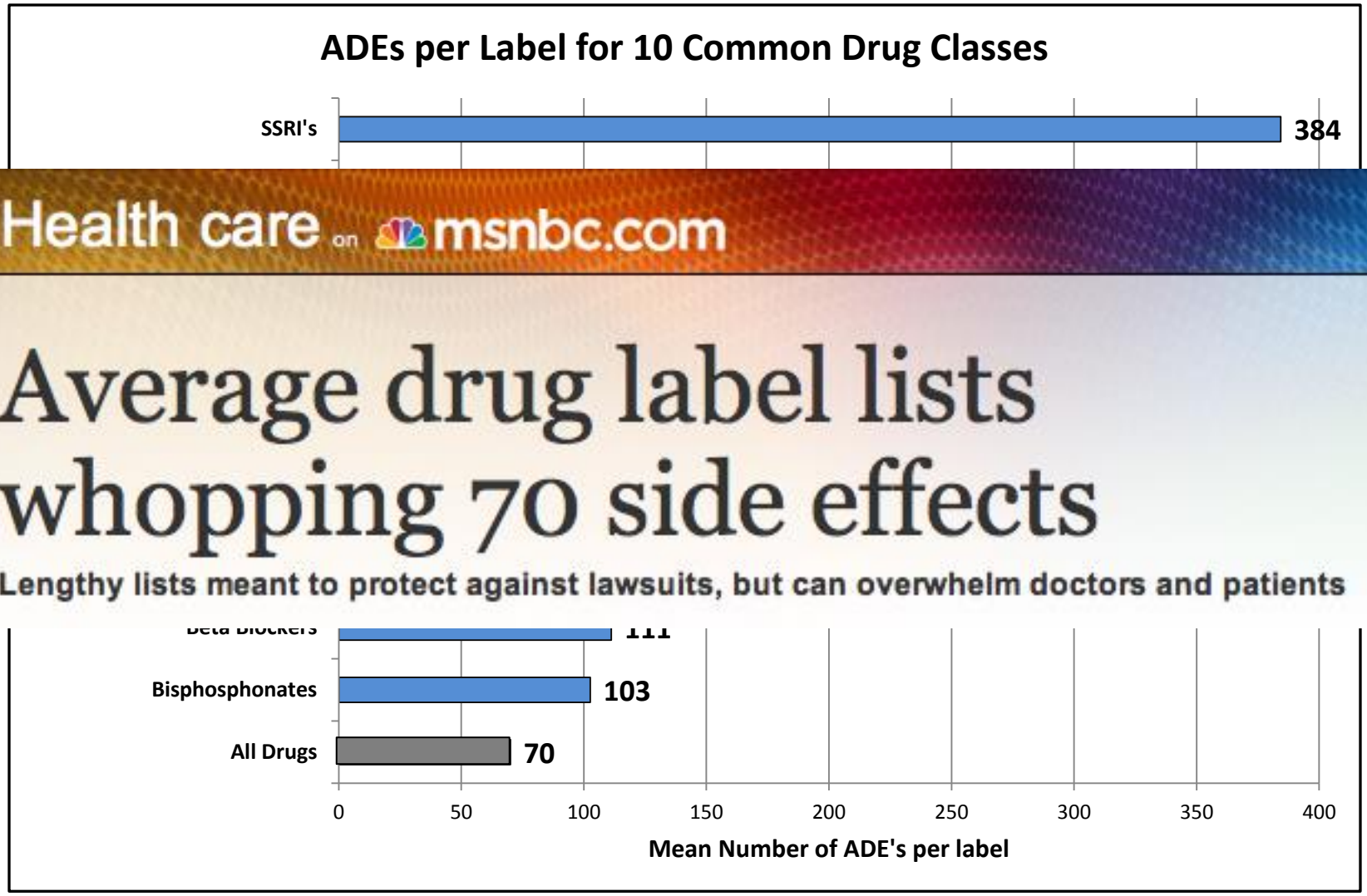
Adverse Reactions

- Nausea (76%)
- Vomiting (69%)
- Headache (66%)
- Dizziness (63%)
- Rash (60%)
- Pruritis (59%)
- Diarrhea (57%)
- Urticaria (51%)
- Fever (46%)

Post-Marketing Events

- Angioedema (29%)
- Stevens-Johnson (24%)
- Hypersensitivity (47%)
- Thrombocytopenia (42%)
- Anaphylactic reaction (28%)
- TEN (21%)
- Erythema multiforme (22%)
- Hepatitis (26%)
- Urticaria (51%)


ADEs per Label for 10 Common Drug Classes
Drug Class
SSRI's
Atypical Antipsychotics
5-HT1 Agonists (Triptans)
Proton Pump Inhibitors
ACE-Inhibitors
Statins
NSAIDs
Benzodiazepines
Beta Blockers
Bisphosphonates
All Drugs
384
241
227
185
165
127
121
118
111
103
70
0
50
100
150
200
250
300
350
400
Mean Number of ADE's per label



Health care on msnbc.com

Average drug label lists whopping 70 side effects

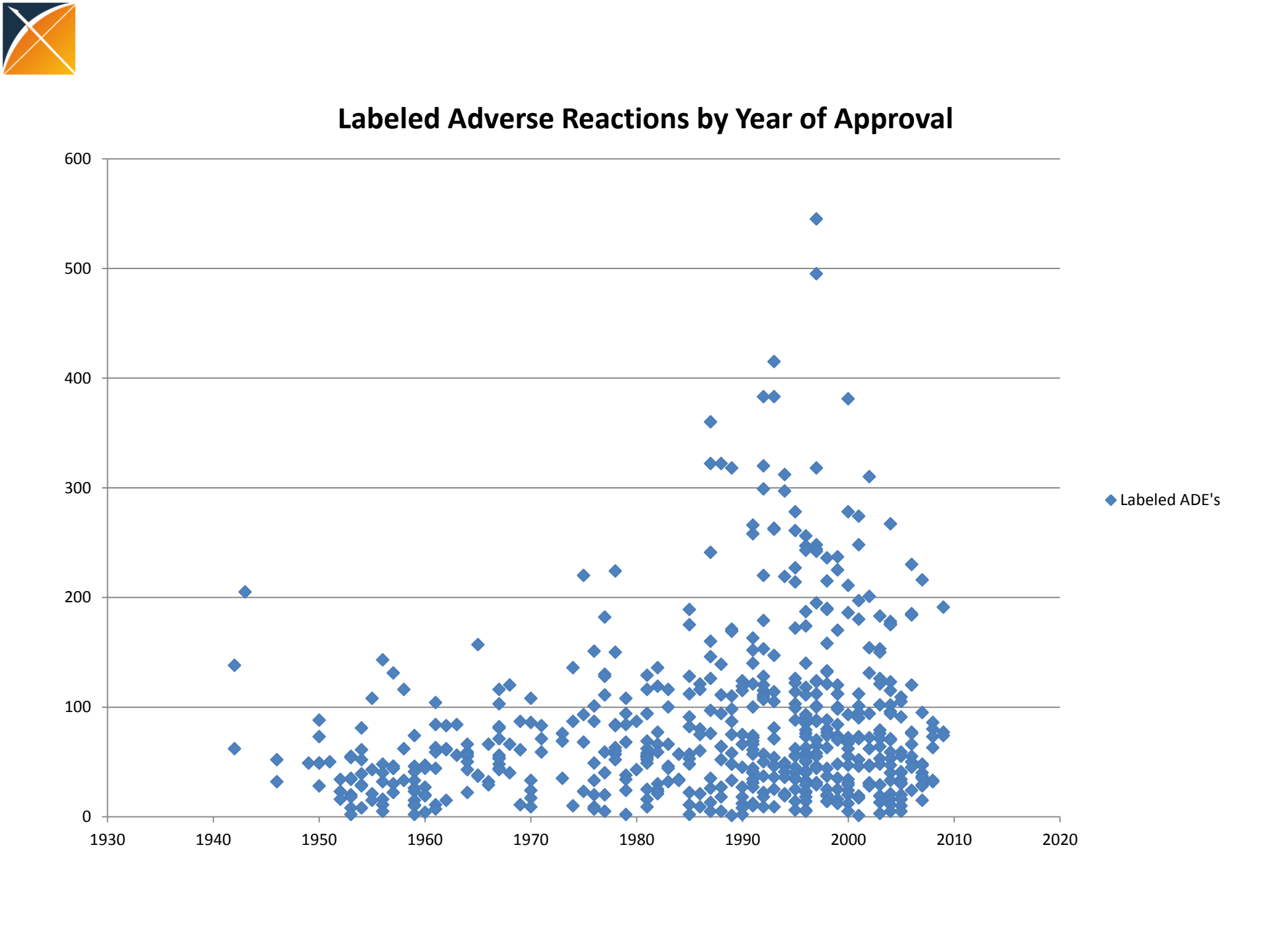
Lengthy lists meant to protect against lawsuits, but can overwhelm doctors and patients

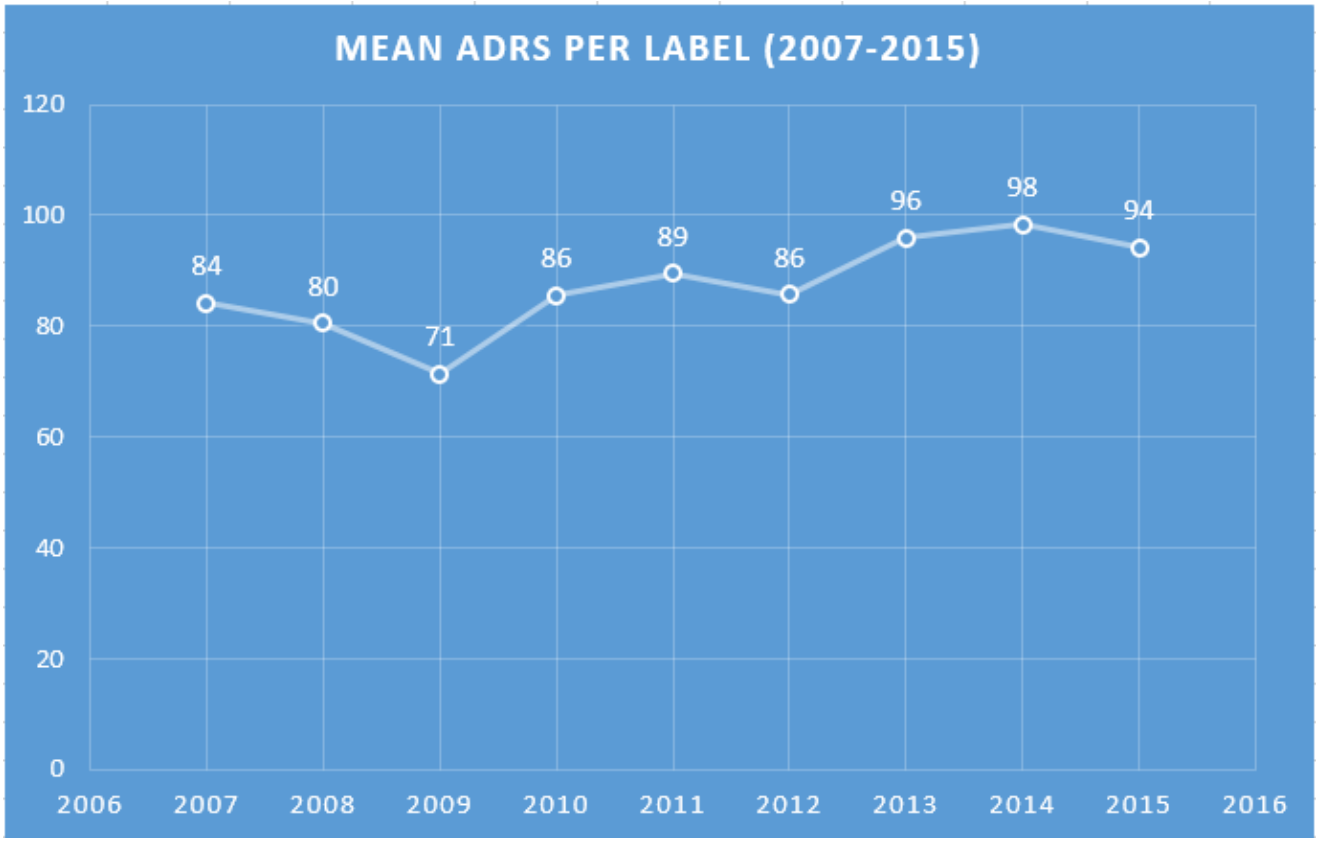
Guidance for Industry

Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products — Content and Format

ADVERSE REACTIONS section includes only information that would be useful to health care practitioners making treatment decisions and monitoring and advising patients. Exhaustive lists of every reported adverse event, including those that are infrequent and minor, commonly observed in the absence of drug therapy or not plausibly related to drug therapy should be avoided (see § 201.57(c)(7) and the Glossary at the end of this guidance for a definition of Adverse Reaction). Such lists are not informative and tend to obscure the more clinically meaningful information.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
January 2006
Labeling


Labeled Adverse Reactions by Year of Approval
600
500
400
300
200
100
0
1930
1940
1950
1960
1970
1980
1990
2000
2010
2020
Labeled ADE's


MEAN ADRS PER LABEL (2007-2015)
120
100
80
60
40
20
0
84
80
71
86
89
86
96
98
94
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016

Other Events Observed During the Premarketing Evaluation of ZOLOFT (sertraline hydrochloride)

Following is a list of treatment-emergent adverse events reported during premarketing assessment of ZOLOFT in clinical trials (over 4000 adult subjects) except those already listed in the previous tables or elsewhere in labeling.

In the tabulations that follow, a World Health Organization dictionary of terminology has been used to classify reported adverse events. The frequencies presented, therefore, represent the proportion of the over 4000 adult individuals exposed to multiple doses of ZOLOFT who experienced an event of the type cited on at least one occasion while receiving ZOLOFT. All events are included except those already listed in the previous tables or elsewhere in labeling and those reported in terms so general as to be uninformative and those for which a causal relationship to ZOLOFT treatment seemed remote. It is important to emphasize that although the events reported occurred during treatment with ZOLOFT, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring on one or more occasions in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients. Events of major clinical importance are also described in the PRECAUTIONS section.

Autonomic Nervous System Disorders–*Frequent* impotence; *Infrequent* flushing, increased saliva, cold clammy skin, mydriasis; *Rare* pallor, glaucoma, priapism, vasodilation.

Body as a Whole–General Disorders–*Rare* allergic reaction, allergy.

Cardiovascular–*Frequent* palpitations, chest pain; *Infrequent* hypertension, tachycardia, postural dizziness, postural hypotension, periorbital edema, peripheral edema, hypotension, peripheral ischemia, syncope, edema, dependent edema; *Rare* precordial chest pain, substernal chest pain, aggravated hypertension, myocardial infarction, cerebrovascular disorder.

Central and Peripheral Nervous System Disorders–*Frequent* hypertonia, hypoesthesia; *Infrequent* twitching, confusion, hyperkinesia, vertigo, ataxia, migraine, abnormal coordination, hyperesthesia, leg cramps, abnormal gait, nystagmus, hypokinesia; *Rare* dysphonia, coma, dyskinesia, hypotonia, ptosis, choreoathetosis, hyperreflexia.

Disorders of Skin and Appendages–*Infrequent* pruritus, acne, urticaria, alopecia, dry skin, erythematous rash, photosensitivity reaction, maculopapular rash; *Rare* follicular rash, eczema, dermatitis, contact dermatitis, bullous eruption, hypertrichosis, skin discoloration, pustular rash.

Endocrine Disorders–*Rare* exophthalmos, gynecomastia.

Gastrointestinal Disorders–*Frequent* appetite increased; *Infrequent* dysphagia, tooth caries aggravated, eructation, esophagitis, gastroenteritis; *Rare* melena, glossitis, gum hyperplasia, hiccup, stomatitis, tenesmus, colitis, diverticulitis, fecal incontinence, gastritis, rectum hemorrhage, hemorrhagic peptic ulcer, proctitis, ulcerative stomatitis, tongue edema, tongue ulceration.

General–*Frequent* back pain, asthenia, malaise, weight increase; *Infrequent* fever, rigors, generalized edema; *Rare* face edema, aphthous stomatitis.

Hearing and Vestibular Disorders–*Rare* hyperacusis, labyrinthine disorder.

Hematopoietic and Lymphatic–*Rare* anemia, anterior chamber eye hemorrhage.

Liver and Biliary System Disorders–*Rare* abnormal hepatic function.

Metabolic and Nutritional Disorders–*Infrequent* thirst; *Rare* hypoglycemia, hypoglycemia reaction.

Musculoskeletal System Disorders–*Frequent* myalgia; *Infrequent* arthralgia, dystonia, arthrosis, muscle cramps, muscle weakness.

Psychiatric Disorders–*Frequent* yawning, other male sexual dysfunction, other female sexual dysfunction; *Infrequent* depression, amnesia, paronirla, teeth-grinding, emotional lability, apathy, abnormal dreams, euphoria, paranoid reaction, hallucination, aggressive reaction, aggravated depression, delusions; *Rare* withdrawal syndrome, suicide ideation, libido increased, somnambulism, illusion.

Reproductive–*Infrequent* menstrual disorder, dysmenorrhea, intermenstrual bleeding, vaginal hemorrhage, amenorrhea, leukorrhea; *Rare* female breast pain, menorrhagia, balanoposthitis, breast enlargement, atrophic vaginitis, acute female mastitis.

Respiratory System Disorders–*Frequent* rhinitis; *Infrequent* coughing, dyspnea, upper respiratory tract infection, epistaxis, bronchospasm, sinusitis; *Rare* hyperventilation, bradypnea, stridor, apnea, bronchitis, hemoptysis, hypoventilation, laryngismus, laryngitis.

Special Senses–*Frequent* tinnitus; *Infrequent* conjunctivitis, earache, eye pain, abnormal accommodation; *Rare* xerophthalmia, photophobia, diplopia, abnormal lactination, scotoma, visual field defect.

Urinary System Disorders–*Infrequent* micturition frequency, polyuria, urinary retention, dysuria, nocturia, urinary incontinence; *Rare* cystitis, oliguria, pyelonephritis, hematuria, renal pain, strangury.

Incidence of Adverse Events in Short-Term, Placebo-Controlled and Combination Trials

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Bipolar Mania Monotherapy — Overall, there was no difference in the incidence of discontinuation due to adverse events (2% for oral olanzapine vs 2% for placebo).

Agitation — Overall, there was no difference in the incidence of discontinuation due to adverse events (0.4% for intramuscular olanzapine for injection vs 0% for placebo).

Adverse Events Associated with Discontinuation of Treatment in Short-Term Combination Trials

Bipolar Mania Combination Therapy — In a study of patients who were already tolerating either lithium or valproate as monotherapy, discontinuation rates due to adverse events were 11% for the combination of oral olanzapine with lithium or valproate compared to 2% for patients who remained on lithium or valproate monotherapy. Discontinuations with the combination of oral olanzapine and lithium or valproate that occurred in more than 1 patient were: somnolence (3%), weight gain (1%), and peripheral edema (1%).

Commonly Observed Adverse Events in Short-Term, Placebo-Controlled Trials

The most commonly observed adverse events associated with the use of oral olanzapine (incidence of 5% or greater) and not observed at an equivalent incidence among placebo-treated patients (olanzapine incidence at least twice that for placebo) were:

Common Treatment-Emergent Adverse Events Associated with the Use of Oral Olanzapine in 6-Week Trials — SCHIZOPHRENIA

Adverse Event	Percentage of Patients Reporting Event	
	Olanzapine (N=248)	Placebo (N=119)
Postural hypotension	5	2
Constipation	9	3
Weight gain	6	1
Dizziness	11	4
Personality disorder*	8	4
Akathisia	5	1

* Personality disorder is the COSTART term for designating non-aggressive objectionable behavior.

Common Treatment-Emergent Adverse Events Associated with the Use of Oral Olanzapine in 3-Week and 4-Week Trials — BIPOLAR MANIA

Adverse Event	Percentage of Patients Reporting Event	
	Olanzapine (N=128)	Placebo (N=129)
Asthenia	18	6
Dry mouth	22	7
Constipation	11	6
Dyspepsia	11	6
Increased appetite	6	3
Somnolence	55	13
Dizziness	18	6
Tremor	6	3

TABLE 3 TREATMENT-EMERGENT ADVERSE EVENTS: INCIDENCE IN PLACEBO-CONTROLLED CLINICAL TRIALS Percentage of Patients Reporting Event Major Depressive Disorder/Other[†], OCD, Panic Disorder, PTSD, PMDD and Social Anxiety Disorder combined

Body System/Adverse Event[‡]	ZOLOFT (N=2799)	Placebo (N=2394)
Autonomic Nervous System Disorders		
Ejaculation Failure[§]	14	1
Mouth Dry	14	8
Sweating Increased	7	2
Centor. & Periph. Nerv. System Disorders		
Somnolence	13	7
Dizziness	12	7
Headache	26	23
Paresthesia	2	1
Tremor	8	2
Disorders of Skin and Appendages		
Rash	3	2
Gastrointestinal Disorders		
Anorexia	6	2
Constipation	6	4
Diarrhea/Loose Stools	20	10
Dyspepsia	8	4
Nausea	26	11
Vomiting	4	2
General		
Fatigue	12	7
Psychiatric Disorders		
Agitation	5	3
Anxiety	4	3
Insomnia	21	11
Libido Decreased	6	2
Nervousness	5	4
Special Senses		
Vision Abnormal	3	2

† Major depressive disorder and other premarketing controlled trials.
‡ Included are events reported by at least 2% of patients taking ZOLOFT except the following events, which had an incidence on placebo greater than or equal to ZOLOFT: abdominal pain, back pain, flatulence, malaise, pain, pharyngitis, respiratory disorder, upper respiratory tract infection.
§ Primarily ejaculatory delay. Denominator used was for male patients only (N=1118 ZOLOFT, N=926 placebo).

Other Events Observed During the Premarketing Evaluation of ZOLOFT (sertraline hydrochloride)

Following is a list of treatment-emergent adverse events reported during premarketing assessment of ZOLOFT in clinical trials (over 4000 adult subjects) except those already listed in the previous tables or elsewhere in labeling.

In the tabulations that follow, a World Health Organization dictionary of terminology has been used to classify reported adverse events. The frequencies presented, therefore, represent the proportion of the over 4000 adult individuals exposed to multiple doses of ZOLOFT who experienced an event of the type cited on at least one occasion while receiving ZOLOFT. All events are included except those already listed in the previous tables or elsewhere in labeling and those reported in terms so general as to be uninformative and those for which a causal relationship to ZOLOFT treatment seemed remote. It is important to emphasize that although the events reported occurred during treatment with ZOLOFT, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring on one or more occasions in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients. Events of major clinical importance are also described in the PRECAUTIONS section.

Autonomic Nervous System Disorders–*Frequent* impotence; *Infrequent* flushing, increased saliva, cold clammy skin, mydriasis; *Rare* pallor, glaucoma, priapism, vasodilation.

Body as a Whole–General Disorders–*Rare* allergic reaction, allergy.

Cardiovascular–*Frequent* palpitations, chest pain; *Infrequent* hypertension, tachycardia, postural dizziness, postural hypotension, periorbital edema, peripheral edema, hypotension, peripheral ischemia, syncope, edema, dependent edema; *Rare* precordial chest pain, substernal chest pain, aggravated hypertension, myocardial infarction, cerebrovascular disorder.

Central and Peripheral Nervous System Disorders–*Frequent* hypertonia, hypoesthesia; *Infrequent* twitching, confusion, hyperkinesia, vertigo, ataxia, migraine, abnormal coordination, hyperesthesia, leg cramps, abnormal gait, nystagmus, hypokinesia; *Rare* dysphonia, coma, dyskinesia, hypotonia, ptosis, choreoathetosis, hyperreflexia.

Disorders of Skin and Appendages–*Infrequent* pruritus, acne, urticaria, alopecia, dry skin, erythematous rash, photosensitivity reaction, maculopapular rash; *Rare* follicular rash, eczema, dermatitis, contact dermatitis, bullous eruption, hypertrichosis, skin discoloration, pustular rash.

Endocrine Disorders–*Rare* exophthalmos, gynecomastia.

Gastrointestinal Disorders–*Frequent* appetite increased; *Infrequent* dysphagia, tooth caries aggravated, eructation, esophagitis, gastroenteritis; *Rare* melena, glossitis, gum hyperplasia, hiccup, stomatitis, tenesmus, colitis, diverticulitis, fecal incontinence, gastritis, rectum hemorrhage, hemorrhagic peptic ulcer, proctitis, ulcerative stomatitis, tongue edema, tongue ulceration.

General–*Frequent* back pain, asthenia, malaise, weight increase; *Infrequent* fever, rigors, generalized edema; *Rare* face edema, aphthous stomatitis.

Hearing and Vestibular Disorders–*Rare* hyperacusis, labyrinthine disorder.

Hematopoietic and Lymphatic–*Rare* anemia, anterior chamber eye hemorrhage.

Liver and Biliary System Disorders–*Rare* abnormal hepatic function.

Metabolic and Nutritional Disorders–*Infrequent* thirst; *Rare* hypoglycemia, hypoglycemia reaction.

Musculoskeletal System Disorders–*Frequent* myalgia; *Infrequent* arthralgia, dystonia, arthrosis, muscle cramps, muscle weakness.

Psychiatric Disorders–*Frequent* yawning, other male sexual dysfunction, other female sexual dysfunction; *Infrequent* depression, amnesia, paronirla, teeth-grinding, emotional lability, apathy, abnormal dreams, euphoria, paranoid reaction, hallucination, aggressive reaction, aggravated depression, delusions; *Rare* withdrawal syndrome, suicide ideation, libido increased, somnambulism, illusion.

Reproductive–*Infrequent* menstrual disorder, dysmenorrhea, intermenstrual bleeding, vaginal hemorrhage, amenorrhea, leukorrhea; *Rare* female breast pain, menorrhagia, balanoposthitis, breast enlargement, atrophic vaginitis, acute female mastitis.

Respiratory System Disorders–*Frequent* rhinitis; *Infrequent* coughing, dyspnea, upper respiratory tract infection, epistaxis, bronchospasm, sinusitis; *Rare* hyperventilation, bradypnea, stridor, apnea, bronchitis, hemoptysis, hypoventilation, laryngismus, laryngitis.

Special Senses–*Frequent* tinnitus; *Infrequent* conjunctivitis, earache, eye pain, abnormal accommodation; *Rare* xerophthalmia, photophobia, diplopia, abnormal lactination, scotoma, visual field defect.

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Evaluation
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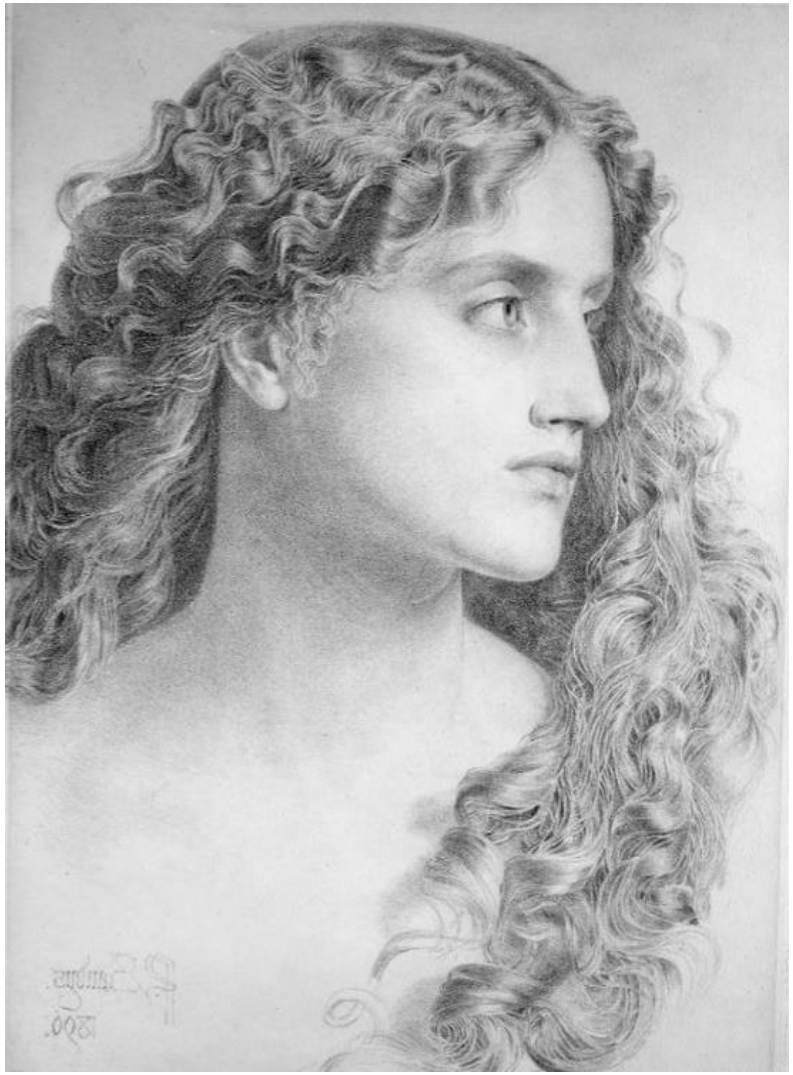
Product
Effects



Geriatric use

Clinical studies of baclofen did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

Sedating drugs may cause confusion and over-sedation in the elderly; elderly patients generally should be started on low doses of KEMSTROâ¢ and observed closely.

Adverse Reactions

The most common adverse reaction during treatment with baclofen is transient drowsiness (10-63%). In one controlled study of 175 patients, transient drowsiness was observed in 63% of those receiving baclofen tablets compared to 36% of those in the placebo group. Other common adverse reactions are dizziness (5-15%), weakness (5-15%) and fatigue (2-4%). Others reported:

Neuropsychiatric: Confusion (1-11%), headache (4-8%), insomnia (2-7%); and, rarely, euphoria, excitement, depression, hallucinations, paresthesia, muscle pain, tinnitus, slurred speech, coordination disorder, tremor, rigidity, dystonia, ataxia, blurred vision, nystagmus, strabismus, miosis, mydriasis, diplopia, dysarthria, epileptic seizure.

Cardiovascular: Hypotension (0-9%). Rare instances of dyspnea, palpitation, chest pain, syncope.

Gastrointestinal: Nausea (4-12%), constipation (2-6%); and, rarely, dry mouth, anorexia, taste disorder, abdominal pain, vomiting, diarrhea, and positive test for occult blood in stool.

Genitourinary: Urinary frequency (2-6%); and, rarely, enuresis, urinary retention, dysuria, impotence, inability to ejaculate, nocturia, hematuria.

Other: Instances of rash, pruritus, ankle edema, excessive perspiration, weight gain, nasal congestion.

Some of the CNS and genitourinary symptoms may be related to the underlying disease rather than to drug therapy. The following laboratory tests have been found to be abnormal in a few patients receiving baclofen: increased SGOT, elevated alkaline phosphatase, and elevation of blood sugar.

PENELOPE

- PENELOPE leverages OHDSI's evidence generation and curation tools to provide context to safety information on drug labels
- The nature of this context may differ for different stakeholders (e.g., providers, researchers, patients)

A Big Supporting Cast

ACHILLES: Database profiling

HERMES: Vocabulary exploration

CIRCE: Cohort definition

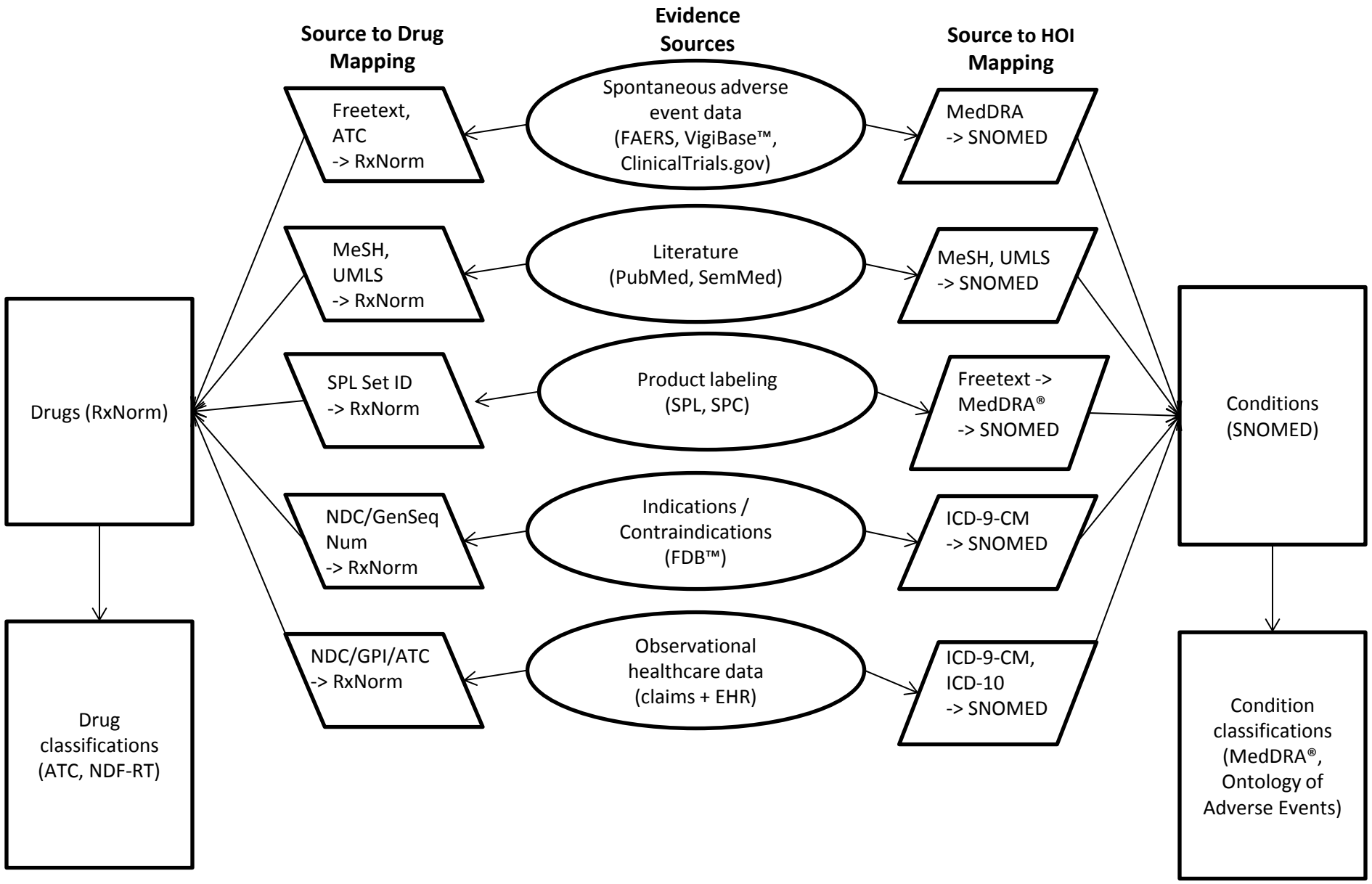
HERACLES: Cohort characterization

LAERTES: Drug-AE evidence base

PLATO: Patient-level predictive modeling

HOMER: Population-level causality assessment

LAERTES


Source to Drug Mapping
Evidence Sources
Source to HOI Mapping
Freetext, ATC -> RxNorm
Spontaneous adverse event data (FAERS, VigiBase™, ClinicalTrials.gov)
MedDRA -> SNOMED
MeSH, UMLS -> RxNorm
Literature (PubMed, SemMed)
MeSH, UMLS -> SNOMED
SPL Set ID -> RxNorm
Product labeling (SPL, SPC)
Freetext -> MedDRA® -> SNOMED
NDC/GenSeq Num -> RxNorm
Indications / Contraindications (FDB™)
ICD-9-CM -> SNOMED
NDC/GPI/ATC -> RxNorm
Observational healthcare data (claims + EHR)
ICD-9-CM, ICD-10 -> SNOMED
Drugs (RxNorm)
Drug classifications (ATC, NDF-RT)
Conditions (SNOMED)
Condition classifications (MedDRA®, Ontology of Adverse Events)

Shall We Take a Look?

PENELOPE - it takes a community!

Anthony Sena
Janssen

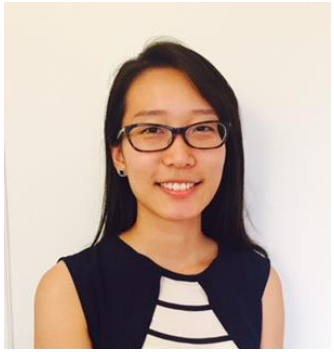
Frank DeFalco
Janssen

Rich Boyce
UPitt

Matt Levine
Columbia

Hamed Abedtash
Indiana U

Wen Zhang
UPitt



Erica Voss
Janssen

Lee Evans
LTC Consulting

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Janssen

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