Pharmacoepidemiology and the Regulation of Medicines

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The opinions expressed in this lecture are those of the presenter, and do not necessarily represent the views of the US Food and Drug Administration or the US Government

No conflicts of interest to disclose
Role of the Drug Regulator

• Access to medicines
  – Assess efficacy, safety, quality

• Protection of the public
  – During clinical trials
  – Postapproval

• Information to the public
Drug Regulation

Science-based

Public-health focused

Regulatory activity

Drug Regulation
Drug Development Timeline

Submit IND

Pre-Human Research

Development Phase

Phase 1

Phase 2

Phase 3

FDA Review

Postmarketing Phase

Submit Application

Approval

Marketing and Phase 4
Sources of Risk From Medical Products

- Known Side Effects
  - Unavoidable
  - Avoidable

- Medication and Device Errors

- Product Defects

Preventable Adverse Events

Injury or Death

Remaining Uncertainties:
- Unexpected side effects
- Unstudied uses
- Unstudied populations
What We Want to Learn

- Learns about new risks
- Learns more about known risks
- Learns about medication errors
- Learns about product defects
- Learns how patterns of use may contribute to unsafe use
Why We Want to Learn It

- So patients and practitioners can make informed choices
- So patients can use medicines properly, effectively, and safely
- So patients and practitioners can monitor treatment both for effectiveness and the development of adverse drug reactions
- So patients and practitioners can modify treatment as needed
- So manufacturers and regulators can make changes to product labels and, if needed, to marketing authorization status
Drug safety knowledge is accrued throughout the lifecycle of a drug

This process is iterative, incremental and essential
Growing Volume of Medication Usage – United States

Nationally Estimated Number of Total Prescriptions Dispensed from U.S. Outpatient Retail Pharmacies

- 2010: 3.54 billion
- 2011: 3.57 billion
- 2012: 3.71 billion
- 2013: 3.81 billion
- 2014: 3.92 billion

Source: National Prescription Audit (NPA™), Years 2010-2014. Extracted November 2015
Public Concern

Failing the Public Health — Rofecoxib, Merck, and the FDA

Eric J. Topol, M.D.

On May 21, 1999, Merck was granted approval by the Food and Drug Administration (FDA) to market rofecoxib (Vioxx). On September 30, 2004, after more than 80 million patients had taken this med-
dial infarctions associated with rofecoxib and the numerical, albeit not statistically significant, ex-
cess associated with celecoxib, was that “it is mand-
datory to conduct a trial specifically assessing car-

VIEWS & REVIEWS

Rosiglitazone and the need for a new drug safety agency

PERSONAL VIEW Silvio Garattini, Vittorio Bertele’

The recent news about the suspension of rosiglitazone, a blockbuster had underestimated or overlooked it. The usual true Europe-wide network such as the current
Increased Focus on Postmarket Drug Safety

- Agency actions to strengthen postmarket drug safety systems
- Institute of Medicine Report 2007
- Passage of the Food and Drug Administration Amendments Act (FDAAA) – September 2007
FDAAA

Public Law 110–85
110th Congress

An Act

To amend the Federal Food, Drug, and Cosmetic Act to revise and extend the user-fee programs for prescription drugs and for medical devices, to enhance the postmarket authorities of the Food and Drug Administration with respect to the safety of drugs, and for other purposes.

Sept. 27, 2007
[H.R. 3580]

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,

SECTION 1. SHORT TITLE.

This Act may be cited as the “Food and Drug Administration Amendments Act of 2007”.

Features

- Landmark legislation
- Increased funding for postmarket drug safety
- Increased transparency

New authorities allowing FDA to require:

- Postmarketing safety studies and clinical trials
- Safety labeling changes
- Risk evaluation and mitigation strategies
Sources of Drug Safety Information

- Spontaneous Adverse Event Reports
- Clinical Trials
- Observational Studies
- Registries
- Clinical Pharmacology Studies
- Pharmacogenomics Studies
- Animal Toxicology Studies
- Product Quality Reports
Pharmacoepidemiology

“Pharmacoepidemiology is the study of the use of and the effects of drugs in large numbers of people.”

(Strom B. Pharmacoepidemiology 5th Ed., 2012)
Some Features of Pharmacoepidemiology

- Exposure is intentional (usually)
- Medicines are usually given to people with an illness
- Prescribing decisions may (and often do) take into account factors that are related to outcomes of interest
- Confounding and bias can be big problems in observational data
  - Confounding by indication
  - Channeling bias
  - Lots of others
Major Methods in Pharmacoepidemiology

- Case Reports
- Case Series
- Observational Studies
- Clinical Trials
Sources of Drug Safety Information

- Spontaneous Adverse Event Reports
- Product Quality Reports
- Clinical Trials
- Observational Studies
- Animal Toxicology Studies
- Pharmacogenomics Studies
- Clinical Pharmacology Studies
- Registries
Historically....

• Case reports were the main source of drug safety information
  – Good for rare events that are usually the result of drug or toxin exposure
    • Acute liver failure
    • Stevens-Johnson Syndrome
    • Torsades de pointes
  • The basis of most drug withdrawals and major safety actions
  • Often lack critical details
  • Underreporting
Case Reports are Important

Percentage of safety-related label changes in the United States by data source - 2010

Table 2. Extent of reporting to FDA for statin-associated hospitalized rhabdomyolysis cases

<table>
<thead>
<tr>
<th>Statin</th>
<th>Number of US prescriptions*</th>
<th>Average days supply per prescription**</th>
<th>US person-years of statin exposure</th>
<th>Cohort study IR† (per person-years)</th>
<th>Estimated number of cases</th>
<th>AERS cases*</th>
<th>Extent of reporting to FDA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin</td>
<td>149 706 000</td>
<td>34.78</td>
<td>14 255 372</td>
<td>6.05 × 10⁻⁵</td>
<td>863</td>
<td>43</td>
<td>5.0%</td>
</tr>
<tr>
<td>Cerivastatin</td>
<td>11 172 000</td>
<td>33.60</td>
<td>1 027 732</td>
<td>1.32 × 10⁻³</td>
<td>1357</td>
<td>424</td>
<td>31.2%</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>83 673 000</td>
<td>34.52</td>
<td>7 676 902</td>
<td>0</td>
<td>0</td>
<td>17</td>
<td>—</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>120 188 000</td>
<td>34.95</td>
<td>11 500 535</td>
<td>7.23 × 10⁻⁵</td>
<td>832</td>
<td>118</td>
<td>14.2%</td>
</tr>
<tr>
<td>All four statins</td>
<td>364 739 000</td>
<td>34.84</td>
<td>34 791 257</td>
<td>9.78 × 10⁻⁵</td>
<td>3403</td>
<td>602</td>
<td>17.7%</td>
</tr>
<tr>
<td>Atorvastatin, pravastatin, simvastatin</td>
<td>353 567 000</td>
<td>34.88</td>
<td>33 764 317</td>
<td>5.31 × 10⁻⁵</td>
<td>1793</td>
<td>178</td>
<td>9.9%</td>
</tr>
</tbody>
</table>

IR, incidence rate; AERS, Adverse Event Reporting System.
*Reference 9.
**Average days supply per prescription in the US during the study period from Verispan LLC, VONA. Data extracted 7/8/2006.
†Reference 9.

Sources of Drug Safety Information

- Spontaneous Adverse Event Reports
- Clinical Trials
- Observational Studies
- Registries
- Clinical Pharmacology Studies
- Pharmacogenomics Studies
- Animal Toxicology Studies
- Product Quality Reports
Natalizumab - Approval

- Integrin receptor antagonist
  - Binds to α4-subunit of α4β1 and α4β7 integrins
- Initially approved to reduce frequency of clinical exacerbations in patients with relapsing form of multiple sclerosis
- Routine monitoring in place

Approved
23 November 2004
Natalizumab – First Cases of PML

- Within three months of approval, two cases of progressive multifocal leukoencephalopathy (PML) reported in multiple sclerosis patients
- PML is a rare, serious, progressive neurologic disease, usually occurring in immunosuppressed patients, often resulting in irreversible neurologic deterioration and death.
- Marketing was suspended
- Intensive evaluation of all data

Approved
23 November 2004

Marketing suspended
28 February 2005

Routine PV | Intensive Evaluation
Natalizumab – Marketing Resumed

- Intensive evaluation revealed no additional cases in multiple sclerosis patients
- FDA sought input from experts and the public, including patients

Marketing was resumed with strict risk management
- Restricted distribution
- Pre-infusion evaluations
- Registry of all patients

Continuous risk management, monitoring, and re-assessment
Natalizumab – Update on Treatment Duration

- Label updated in February 2010 to include duration of treatment as a risk factor for PML
- Based on 31 cases of PML in about 66,000 treated patients

In the postmarketing setting, additional cases of PML have been reported in multiple sclerosis patients who were receiving no concomitant immunomodulatory therapy. In patients treated with TYSABRI, the risk of developing PML increases with longer treatment duration, and for patients treated for 24 to 36 months is generally similar to the rates seen in clinical trials. There is limited experience beyond 3 years of treatment. There are no known interventions that can reliably prevent PML or adequately treat PML if it occurs. It is not known whether early detection of PML and discontinuation of TYSABRI will mitigate the disease.
Natalizumab – Update on Prior Immunosuppression

- Label updated in April 2011 to include prior immunosuppression as a risk factor for PML
- Based on 102 cases of PML in about 82,732 treated patients

In the postmarketing setting, additional cases of PML have been reported in multiple sclerosis patients who were receiving no concomitant immunomodulatory therapy. In patients treated with TYSABRI, the risk of developing PML increases with longer treatment duration.

<table>
<thead>
<tr>
<th>Duration of Therapy (Number of Infusions)</th>
<th>PML Incidence per 1,000 Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Up to 24</td>
<td>0.3</td>
</tr>
<tr>
<td>25-36</td>
<td>1.5</td>
</tr>
<tr>
<td>37-48</td>
<td>0.9</td>
</tr>
</tbody>
</table>

Table 1: Estimated Incidence of PML in the Postmarketing Setting

The risk of PML is also increased in patients who have been treated with an immunosuppressant (not including prior treatment with short courses of corticosteroids) prior to receiving TYSABRI.

Continuous risk management, monitoring, and re-assessment
Natalizumab – Update on JC Virus Antibody Positivity

- Label updated in January 2012 to include antibodies to JC virus as a risk factor for PML
- Based on 201 cases of PML in about 96,582 treated patients

In the postmarketing setting, additional cases of PML have been reported in multiple sclerosis and Crohn’s disease patients who were receiving no concomitant immunomodulatory therapy. Three factors that are known to increase the risk of PML in TYSABRI-treated patients have been identified:

- Longer treatment duration, especially beyond 2 years. There is limited experience in patients who have received more than 4 years of TYSABRI treatment.
- Prior treatment with an immunosuppressant (e.g., mitoxantrone, azathioprine, methotrexate, cyclophosphamide, mycophenolate mofetil).
- The presence of anti-JCV antibodies. Patients who are anti-JCV antibody positive have a higher risk for developing PML.
Natalizumab – More Updates

- Label updated in May 2015 to include most recent data on risk factors for PML

Table 1: Estimated United States Incidence of PML Stratified by Risk Factor

<table>
<thead>
<tr>
<th>Anti-JCV Antibody Negative</th>
<th>TYSABRI Exposure†</th>
<th>Anti-JCV Antibody Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Prior Immunosuppressant Use</td>
<td>Prior Immunosuppressant Use</td>
<td></td>
</tr>
<tr>
<td>&lt;1/1,000</td>
<td>1/1,000</td>
<td>1/1,000</td>
</tr>
<tr>
<td>1-24 months</td>
<td>&lt;1/1,000</td>
<td>1/1,000</td>
</tr>
<tr>
<td>25-48 months</td>
<td>3/1,000</td>
<td>12/1,000</td>
</tr>
<tr>
<td>49-72 months</td>
<td>6/1,000</td>
<td>13/1,000</td>
</tr>
</tbody>
</table>

Notes: The risk estimates are based on postmarketing data in the United States from approximately 69,000 TYSABRI exposed patients.
†Data beyond 6 years of treatment are limited.
The anti-JCV antibody status was determined using an anti-JCV antibody test (ELISA) that has been analytically and clinically validated and is configured with detection and inhibition steps to confirm the presence of JCV-specific antibodies with an analytical false negative rate of 3%.
Natalizumab – Summary

- **Iterative**
  - One finding leads to another

- **Incremental**
  - One step at a time

- **Essential**
  - Needed for the safe use of the drug

**Timeline:**

- Approved: 23 November 2004
- Marketing suspended: 28 February 2005
- Marketing resumed: 05 June 2006
- Label updated: 05 February 2010
- Label updated: 22 April 2011
- Label updated: 20 January 2012
- Label updated: 12 May 2015

**PV:** Routine, Intensive Evaluation

Continuous risk management, monitoring, and re-assessment
Sources of Drug Safety Information

- Clinical Trials
- Spontaneous Adverse Event Reports
- Product Quality Reports
- Clinical Pharmacology Studies
- Registries
- Observational Studies
- Pharmacogenomics Studies
- Animal Toxicology Studies
Effect of Sibutramine on Cardiovascular Outcomes in Overweight and Obese Subjects

W. Philip T. James, M.D., D.Sc., Ian D. Caterson, M.D., Ph.D., Walmir Coutinho, M.D., D.Sc., Nick Finer, M.B., B.S., Luc F. Van Gaal, M.D., Ph.D., Aldo P. Maggioni, M.D., Christian Torp-Pedersen, M.D., Ph.D., Arya M. Sharma, M.D., Ph.D., Gillian M. Shepherd, B.Sc., Richard A. Rode, Ph.D., and Cheryl L. Renz, M.D., for the SCOUT Investigators

- Randomized, double-blind, placebo-controlled clinical trial
- Subjects with high cardiovascular risk
- 6-week lead-in sibutramine for all subjects
- 4906 – sibutramine; 4898 – placebo
- Primary endpoint – time to first occurrence of nonfatal myocardial infarction, nonfatal stroke, resuscitation after cardiac arrest, or cardiovascular death


- Mean duration of follow-up – 3.4 years
- Mean lead-in weight change – 2.6 kg loss
- Post-randomization weight change:
  - 1.7 kg loss at 12 months – sibutramine
  - 0.7 kg gain – placebo
- Primary outcome event:
  - 11.4% - sibutramine
  - 10.0% - placebo
  - HR = 1.16 (1.03-1.31), P=0.02
Sources of Drug Safety Information

- Spontaneous Adverse Event Reports
- Clinical Trials
- Observational Studies
- Product Quality Reports
- Drug Safety Information
- Animal Toxicology Studies
- Pharmaco-genomics Studies
- Clinical Pharmacology Studies
- Registries
Today....

- Large databases are available for drug safety studies
- We can detect much more subtle adverse drug effects including increases in relatively common events
  - Common in the population
  - Manifestation of the disease being treated
Observational Studies - I

Azithromycin and the Risk of Cardiovascular Death
Wayne A. Ray, Ph.D., Katherine T. Murray, M.D., Kathi Hall, B.S., Patrick G. Arbogast, Ph.D., and C. Michael Stein, M.B., Ch.B.

- Retrospective cohort study using Tennessee Medicaid
- Excluded patients at high risk for death from unrelated causes
- Patients who took:
  - Azithromycin (347,795 prescriptions)
  - No antibiotics (1,391,180 prescriptions)
  - Amoxicillin (1,348,672 prescriptions)
  - Ciprofloxacin (264,626 prescriptions)
  - Levofoxacin (193,906 prescriptions)

- Five- and ten-day follow-up periods
- End points:
  - Cardiovascular death
  - Death from any cause
- Propensity-score matching
- Complicated methods
- Lots of careful analyses

Observational Studies - II

QT Prolongation
Prolonged cardiac repolarization and QT interval, imparting a risk of developing cardiac arrhythmia and torsades de pointes, have been seen in treatment with macrolides, including azithromycin. Cases of torsades de pointes have been spontaneously reported during postmarketing surveillance in patients receiving azithromycin. Providers should consider the risk of QT prolongation which can be fatal when weighing the risks and benefits of azithromycin for at-risk groups including:

- patients with known prolongation of the QT interval, a history of torsades de pointes, congenital long QT syndrome, bradycardias or uncompensated heart failure
- patients on drugs known to prolong the QT interval
- patients with ongoing proarrhythmic conditions such as uncorrected hypokalemia or hypomagnesemia, clinically significant bradycardia, and in patients receiving Class IA (quinidine, procainamide) or Class III (dofetilide, aminodarone, sotalol) antiarrhythmic agents.

Elderly patients may be more susceptible to drug-associated effects on the QT interval.

Source: US Prescribing Information for Zithromax

- Cardiovascular death:
  - HR = 2.88 (1.79-4.63) (azithromycin vs no antibiotic)
  - HR = 0.95 (0.55-1.63) (amoxicillin vs no antibiotic)
  - HR = 2.49 (1.38-4.50) (azithromycin vs amoxicillin) (Days 1-5)
  - HR = 0.95 (0.44-2.06) (azithromycin vs amoxicillin) (days 6-10)

- Non-cardiovascular death:
  - HR = 0.74 (0.33-1.67) (azithromycin vs no antibiotic)
  - HR = 0.76 (0.42-1.37) (amoxicillin vs no antibiotic)


“...there was a small absolute increase in cardiovascular deaths. As compared with amoxicillin, there were 47 additional cardiovascular deaths per 1 million courses of azithromycin therapy; for patients in the highest decile of baseline risk of cardiovascular disease, there were 245 additional cardiovascular deaths per 1 million courses.”
Observational Studies - Challenges

• Need good data sources
  – Large data sources are not always the best sources

• Need robust methods to adjust for confounders
  – Residual confounding can still be a problem

• If the database is large enough, ANY finding can be statistically significant
  – Need careful interpretation
Effect Measures -- A Not-so-random Sample of Some Recent Drug Safety Issues

- Rosiglitazone - MI – FDA RTC meta-analysis – OR
- PPI - Hip Fracture – Case-Control Study #1 – OR
- PPI - Hip Fracture – Case-Control Study #2 – OR
- Oral Bisphosphonates - Esophageal Cancer – Nested Case-Control Study – RR
- Oral Bisphosphonates - Esophageal Cancer – Cohort Study – HR
- Drosperinone - VTE – Cohort Study – HR

Sources:
Class Effects

• Some adverse effects of a drug occur with all members of class
  – Often related to the class’ pharmacology

• The main question for pharmacoepidemiologists:
  – Can we quantify within-class differences in the risk of the adverse event?
Comparative Risks of Venous Thromboembolism

Figure 1: VTE Risk with Yasmin Relative to LNG-Containing COCs (adjusted risk*)

Risk ratios displayed on logarithmic scale; risk ratio < 1 indicates a lower risk of VTE for DRSP, > 1 indicates an increased risk of VTE for DRSP.

*Comparators “Other COCs”, including LNG-containing COCs
† LASS is an extension of the EURAS study

#Some adjustment factors are indicated by superscript letters: a) Current heavy smoking, b) hypertension, c) obesity, d) family history, e) age, f) BMI, g) duration of use, h) VTE history, i) period of inclusion, j) calendar year, k) education, l) length of use, m) parity, n) chronic disease, o) concomitant medication, p) smoking, q) duration of exposure, r) site


Source: US Prescribing Information for Yasmin
Comparing Risks of Venous Thromboembolism

drospirenone/ethinyl estradiol

Figure 1: VTE Risk with Yasmin Relative to LNG-Containing COCs (adjusted risk)

- Ingenix (Hazard Ratio[^a][^b])
- EURAS (Hazard Ratio[^a][^c])
- LASS (Hazard Ratio[^a][^c])
- FDA-funded study (Hazard Ratio[^a][^d])
- Danish (Rate Ratio[^a][^e])
- Danish re-analysis (Rate Ratio[^a][^e])
- MEGA study (Odds Ratio[^a][^f])
- German case-control (Odds Ratio[^a][^f])
- PharMetrics (Odds Ratio[^a][^f])
- GPRD study (Odds Ratio[^a][^f])

Prospective Cohort Studies
Retrospective Cohort Studies
Case-Control Studies
Non-fatal idiopathic cases only

Risk ratios displayed on logarithmic scale; risk ratio < 1 indicates a lower risk of VTE for DRSP, > 1 indicates an increased risk of VTE for DRSP.

[^a]: Comparator 'Other COCs', including LNG-containing COCs
[^b]: Hazard Ratio
[^c]: Hazard Ratio
[^d]: Hazard Ratio
[^e]: Rate Ratio
[^f]: Odds Ratio

All estimates took account of new-user status. The method and time period used to identify “new users” varied from study to study.


noretgestromin /ethinyl estradiol transdermal system

Figure 1: VTE Risk of ORTHO EVRA Relative to Combined Oral Contraceptives

- Study: i3 Ingenix NGM/Datamart
- Study: BCDS LNP/Pharmetrics
- Study: BCDS LNG/Marketscan
- Study: FDA-funded study
- Study: LNG/30 mcg EE

Source: US Prescribing Information for Yasmin

Source: US Prescribing Information for Ortho-Evra
Putting the Risk Data in Perspective

Figure 2: Likelihood of Developing a VTE

- Non-Pregnant Non-COC user: Ranges from 1 to 5
- COC-User: Ranges from 3 to 9
- Pregnancy *: Ranges from 5 to 20
- Postpartum (12 weeks only): Ranges from 40 to 65

* Pregnancy data based on actual duration of pregnancy in the reference studies. Based on a model assumption that pregnancy duration is nine months, the rate is 7 to 27 per 10,000 WY.

Source: US Prescribing Information for Yasmin
5 WARNINGS AND PRECAUTIONS

5.1 Thromboembolic Disorders and Other Vascular Problems

Stop Yasmin if an arterial or venous thrombotic (VTE) event occurs.

Based on presently available information on Yasmin, DRSP-containing COCs may be associated with a higher risk of venous thromboembolism (VTE) than COCs containing the progestin levonorgestrel or some other progestins. Epidemiologic studies that compared the risk of VTE reported that the risk ranged from no increase to a three-fold increase. Before initiating use of Yasmin in a new COC user or a woman who is switching from a contraceptive that does not contain DRSP, consider the risks and benefits of a DRSP-containing COC in light of her risk of a VTE. Known risk factors for VTE include smoking, obesity, and family history of VTE, in addition to other factors that contraindicate use of COCs [see Contraindications (4)].
The Sentinel System
Sentinel utilizes secondary data

- Patient interaction with the U.S. HealthCare System generates data

- Why is data collected?
  - Payment/billing
  - Document clinical care
  - Physician decision support
  - Recordkeeping

  - Data provide rich source of information for patient safety evaluations
Sentinel uses data and expertise from multiple sources

Lead – HPHC Institute

Data and scientific partners

Scientific partners
Sentinel captures billions of encounters with the healthcare system

- Populations with well-defined person-time for which most medically-attended events are known
  - 334 million person-years of observation time
  - 40 million people currently accruing new data
  - 4.4 billion dispensings
  - 5.1 billion unique encounters
  - 31 million people with ≥1 laboratory test result

** Counts distinct “PatID” values in the database, 2000-2015
Analysis in Sentinel’s distributed data network

1- User creates and submits query (a computer program)

2- Data partners retrieve query

3- Data partners review and run query against their local data

4- Data partners review results

5- Data partners return results via secure network

6- Results are aggregated
Dabigatran and Bleeding Complications

• Approved October 19, 2010 indication of non-valvular atrial fibrillation

• Anticipating a protocol based assessment in Mini-Sentinel at time of approval

• Large number of spontaneous adverse event reports
  – A large number of reports is expected for drugs new to the market compared to other drugs on the market for many years
  – Determine if we could use rapid query in Mini-Sentinel to put a potential bound on risk

• Modular program feature of Mini-Sentinel
FAERS Reports with Dabigatran and Warfarin:
October 19 2010 - October 5, 2011

Total number of reports

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>10133</td>
<td>3460</td>
</tr>
</tbody>
</table>

Serious outcome

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>4251</td>
<td>2617</td>
</tr>
</tbody>
</table>

Death outcome

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>586</td>
<td>318</td>
</tr>
</tbody>
</table>
ICH and GI Bleeding Outcomes/Events – Analysis in Mini-Sentinel

• New users of dabigatran and warfarin
  – During 183 days prior to index dispensing:
    • No dispensings of either dabigatran or warfarin
    • No occurrence of ICH or GIH in in-patient or emergency room setting
    • Require a diagnosis of atrial fibrillation in any healthcare setting

• Incidence Rate = events / 100,000 days at risk

• Additional analyses
  – Define new use by single drug
  – Without the atrial fibrillation requirement
  – Using 365 days instead of 183 days
Intracranial (ICH) and Gastrointestinal (GIH) Bleeding Events in New Users of Dabigatran and Warfarin: Mini-Sentinel (Oct 2010 – Dec 2011, Incidence Rate =New Events/100,000 Days at Risk)

<table>
<thead>
<tr>
<th></th>
<th>Pre-existing Cond. Requirement</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dabigatran</td>
<td>Incidence Rate</td>
</tr>
<tr>
<td>N 10,569</td>
<td>Atrial Fibrillation – 183 days</td>
<td>2.2</td>
</tr>
<tr>
<td>N 9,216</td>
<td>Atrial Fibrillation – 365 days</td>
<td>2.2</td>
</tr>
<tr>
<td>N 12,161</td>
<td>No requirement – 183 days</td>
<td>2.4</td>
</tr>
<tr>
<td>N 10,464</td>
<td>No requirement – 365 days</td>
<td>2.5</td>
</tr>
</tbody>
</table>
**Gastrointestinal (GIH) Bleeding Events in New Users of Dabigatran and Warfarin: Mini-Sentinel**  
(Oct 2010 – Dec 2011, Incidence Rate = New Events/100,000 Days at Risk)

<table>
<thead>
<tr>
<th>Dabigatran</th>
<th>Pre-existing Cond. Requirement</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>Incidence Rate</td>
<td>N</td>
</tr>
<tr>
<td>10,599</td>
<td>1.6</td>
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</table>
Current Challenges

• Deciding what questions need to be answered
• Deciding the best way to answer them
• Understanding the trade-offs in various approaches
• Ethical considerations
• Communications
• Regulatory actions
Traditional Hierarchy of Evidence
From Traditional Hierarchy to Synthesis of Evidence

Traditional hierarchy

Observational Studies

Clinical Trials

Clinical Pharmacology
Toxicology
Other Data

Synthesis of evidence
Pathways to the Abuse/Misuse of Prescription Drugs

Drug manufactured → Drug distributed → Drug prescribed → Drug dispensed → Patient supply → Inappropriate use → Abuse

Drug diversion

Misuse

Addiction

Overdose

Death
How Do We Quantify and Compare Abuse Between Products?

• No national abuse surveillance system for pharmaceutical products

• Abuse ratios (“abuse rates”) are computed to estimate risk of abuse in the population and compare between products

• Numerators and denominators come from separate data sources

• These estimates are crude, but they are the only measures currently available
The Ideal Data System would be...

- Flexible and expandable beyond opioids
- Timely, with data updates every 6 months
- Able to correctly and reliably distinguish brands, formulations and routes of abuse
- Able to provide national and regional estimates
- Composed of complementary components
  - Surveillance (e.g., encounters, clinical outcomes)
  - Quantification (stable trends over time)
  - Impact (linkage with law enforcement, other data)
- But does not currently exist!
Abuse/Misuse-Related Measures of Harm

**Abuse/Misuse-Related Measures of Harm**

### Abuse
- Population Surveys

### Misuse
- Health Care Utilization:
  - Poison control calls
  - ED visits
  - Addiction treatment

### Addiction
- Monitoring the Future
- National Survey on Drug Use and Health

### Overdose
- Drug Abuse Warning Network (to 2011)
- Treatment Episode Data Set
- NAVIPPRO Addiction Severity Index-Multimedia Version

### Death
- Florida Department of Law Enforcement Medical Examiner

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**Abuse/Misuse-Related Measures of Exposure**

- General population
- Kilograms sold
- Total number of dispensed prescriptions
- Total number of unique recipients of dispensed drug
- Total patient-days of therapy
- Total number of tablets dispensed
Abuse Ratios: Poison Control Calls 2006

Denominator = 100 Kgs Sold

Denominator = US Population

Data obtained from DEA Report
DAWN Data Analyzed with Various Denominators – 2007

*OSE Analysis. Sources: Center for Behavioral Health Statistics and Quality, SAMHSA; IMS Health, Vector One®: National (VONA). Extracted 9/08
Measures to quantify the abuse of prescription opioids: a review of data sources and metrics

Alex M. Secora*, Catherine M. Dormitzer, Judy A. Staffa and Gerald J. Dal Pan

Office of Surveillance and Epidemiology, Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, MD, USA

“There is no single best measure of abuse for use as a numerator in an AR, and each must be chosen and interpreted in the context of what it measures.”
Thank you