Pharmacovigilance: Risk Assessment, Management and Communication

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Disclaimer

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Case: GBS and the Flu Vaccine

- 29 April, 2016 – Flu shot administered.
- 1 May, 2016 – Symptoms of Guillain-Barré Syndrome (GBS) develop, patient seeks medical advice.
- 12 May, 2016 – GBS paralysis, difficulty walking, patient seeks medical advice and is accurately diagnosed.
- 16 October, 2016 – Media attention.
Case: GBS and the Flu Vaccine

- How do we assess the risk?
- How do we manage and communicate the risk to patients?

Risk

Benefits

Prevent influenza

Prevent hospitalization

Prevent influenza-related death

GBS ~ 1 in a million
Prescription Drugs Have Risks
Outline

• Understanding drug safety – are clinical trials enough?
• Pharmacovigilance – what is it and why is it important?
• What are the primary components of pharmacovigilance?
  – Risk identification
  – Risk confirmation
  – Risk management
  – Risk communication
Animal studies

Phase 1

Phase 2

Phase 3

Drug approval

Drug Development Process

Human clinical studies

Pre-Marketing

Post-Marketing

Phase 4
Animal studies

Phase 1

Phase 2

Phase 3

Drug approval

Phase 4

**Purpose**

- **Safety** (dose range) in a small number of healthy volunteers
  - 20-80

- **Efficacy** (dose range) in subjects with disease/condition
  - 100’s

- Efficacy and safety in larger population (randomized controlled clinical trials)
  - 1,000’s
Limitations of Pre-Marketing Trials

• Study size
  – Studies with 3,000 patients cannot reliably detect adverse events with an incidence of < 1 per 1000, even if severe.
  – Many drug adverse effects are rare (<1 per 10,000) and will never be detected in clinical trials.
  – When drugs are used in the real world hundreds of thousands of people will get them.
Limitations of Pre-Marketing Trials

- Carefully selected subjects (limited co-morbidities, compliant, limited or no co-medications) may not reflect real-world patients in whom drug will be used.
- Study subjects receive better care/attention than real-world patients.
- Pre-marketing clinical trials are typically of short duration (of treatment).
Contributing Factors

• Push by drug companies and patient advocacy groups to get drugs to market faster – may take shortcuts.

• Pharmaceutical companies and their stockholders may prioritize expansion of market and profits ahead of safety.

• Pharmaceutical companies have been known to attempt to hide safety problems.
The Consequences

• 50% of drugs have a label change due to major safety issues discovered after marketing.

• About 20% of drugs get new “black box” warnings after marketing (thousands in the US).

• About 4% of drugs are ultimately withdrawn for safety reasons (at least 75 in the US, 175 worldwide since 1970).
Bottom-line

• When drugs are first marketed we know little about the potential adverse effects they may have – especially rare effects.

• What are some examples?
Thalidomide

- Sedative/hypnotic, morning sickness cure.
- Caused 2,000 deaths and up to 100,000 cases of phocomelia in children of mothers who used it.
- Not approved by the FDA in the US* but used throughout the world in 1950s, 1960s.
- Prompted many countries to introduce tougher drug testing/licensing rules, including the US.
DES (Diethylestibestrol)

• Synthetic estrogen to prevent miscarriage, premature labor, other pregnancy complications. Later proved not effective.
• On market 1940-1971 (31 years), 3 million pregnant women prescribed DES in the US.
• Caused clear cell carcinoma (vaginal tumor) in girls exposed in utero (DES daughters), and other birth defects. May also effect third generation.
“Really?”

Yes...

desPLEX®

to prevent ABORTION, MISCARRIAGE and PREMATURE LABOR

recommended for routine prophylaxis in ALL pregnancies...

96 per cent live delivery with desPLEX in one series of 1200 patients—
—bigger and stronger babies, too, cf. 1

No gastric or other side effects with desPLEX
— in either high or low dosage.
Redux (Dexfenfluramine)

- Appetite suppressant (called “Fen-Phen” when prescribed with phentermine).
- 30% of patients had abnormal echocardiograms, 100 cases of heart disease.
- $3.75 billion settlement.
Accutane (Isotretinoin)

- Approved for treatment of acne.
- On the market 1982-2009 (27 years)*
- Caused birth defects, miscarriages, premature births in pregnant women.
Darvon and Darvocet (Propoxyphene)

• Opioid pain reliever.
• On the market 1955-2010 (55 years).
• Caused serious heart toxicity, over 2,100 deaths.
Vioxx (Rofecoxib)

- Pain relief (NSAID).
- On the market 1999-2014 (5.3 years).
- Caused 27,785 heart attacks and sudden cardiac death.
Audience Participation: Are Clinical Trials Enough?

Yes

No
Phase 4 is any study that occurs after marketing. For the most part these are not mandated by FDA. Called “post-marketing” studies.
Pharmacovigilance

- **Pharmacovigilance** is a type of continual monitoring for unwanted effects and other safety-related aspects of drugs that are already on the market.
  - Also called “post-marketing surveillance”
  - Pharmacovigilance includes a focus on case reports and spontaneous reporting systems.
  - Pharmacovigilance is generally thought of as a subset of the larger discipline of Pharmacoepidemiology.

- **Pharmacoepidemiology** is “the study of the use and effects (positive and negative) of medications in large numbers of people,” - and in the area of drug safety involves approaches and use of data that are more complex than pharmacovigilance.
The Process of Pharmacovigilance

**STEP 1 - Safety Data**
Case Reports or Other

**STEP 2 - Risk Identification**
Signal Detection
Data Mining

**STEP 3 - Risk Evaluation and Confirmation**
Pharmacoepidemiology

**STEP 4 - Risk Prioritization**
Risk vs. Benefit Analysis

**STEP 5 - Risk Management**
Risk Minimization
Risk Communication
STEP 1: Safety Data

• Spontaneous reports
  – Case Reports → Case series

• Registries
  – Drug or Disease-Based

• Other databases
  – Insurance/administrative claims
  – Electronic medical records
  – Social media
Spontaneous Reports

• Reporting begins with an observation of a untoward event suspected to be caused by a drug.

• Considered “spontaneous” because the reporting is voluntary and passive.

• Single reports can accumulate, become case series, and eventually assessed quantitatively as a “signal”.
MedWatch → FDA
Tarjeta Amarilla ➔ Centro Nacional de Farmacovigilancia (CNFV)
Spontaneous Reports

• Important to generate hypotheses about a drug and effect, signal need for further investigation/caution.

• Pharmacovigilance depends on the quality reports generated by the public and healthcare professionals.
Registries

• A registry follows a group of individuals who all have a specific disease/condition or are receiving a particular drug.

• Drug registries typically allow identification of an adverse effect if it occurs in those exposed to the drug who are enrolled in the registry.

• Prospective, real-world data.

• Allows determination of the rate of the event.

• Not subject to the same limitations for spontaneous reporting systems.
Insurance or Healthcare Databases

- Databases include patient records/claims from inpatient and outpatient care, including diagnoses, therapies used, prescriptions, laboratory tests, etc.
Databases

Administrative/Claims Database
- Generate after contact with the health-care system
  - Hospital, pharmacy, clinic
- Maintained for the purpose of billing or other administrative purposes
- Typically large
- May not capture important clinical information

Medical Record Database
- Use of the patient’s actual electronic medical record (EMR)
  - De-identified in the database
- Maintained for the purpose of clinical patient care
- More likely to capture the true clinical state of the patient
  - Smoking status, BMI, family history
STEP 2: Risk Identification

- Descriptions of individual cases or case series can help qualitatively.
- “Signal detection” requires quantitative approach, requires accumulation of reported cases, typically via a spontaneous adverse event reporting systems.
Signal Detection

- Determine if the event is being reported more often (disproportionally) than expected by comparing to all other drugs in the database.

- **Statistical methods**
  - Numerator-only (data-mining)
    - Disproportionality analyses (PRR, ROR, EBGM, IC)
  - Numerator/denominator
    - Combines cases with an external data as a proxy for exposure.
    - Can calculate the rate of reporting of the event.
    - Compare that to other drugs in the class or other classes.
Examples

Figure 1. Disproportionality analysis with alendronate and *Clostridium difficile* infection. The cumulative empirical Bayes geometric mean (EBGM) from 1997 to 2014 for alendronate and *C. difficile* infection is shown. Dashed line indicates cutoff for drug safety signal. FDA = Food and Drug Administration.

Figure 4. Empirical Bayes rate multiplier estimates and confidence intervals for leukotriene-modifying agents (LTMA$s$) and short-acting beta-agonists (SABA$s$) for the entire time period (1999-2009). A rate multiplier of 1.0 indicates that the drug has the same rate as the average for the other drugs in the analysis, a multiplier of 2.0 is twice the average rate, and a multiplier of 0.5 is half the average rate.
Figure 1. Disproportionality analysis with alendronate and Clostridium difficile infection. The cumulative empirical Bayes geometric mean (EBGM) from 1997 to 2014 for alendronate and C. difficile infection is shown. Dashed line indicates cutoff for drug safety signal. FDA = Food and Drug Administration.

Figure 4. Empirical Bayes rate multiplier estimates and confidence intervals for leukotriene-modifying agents (LTMA) and short-acting beta-agonists (SABAs) for the entire time period (1999-2009). A rate multiplier of 1.0 indicates that the drug has the same rate as the average for the other drugs in the analysis, a multiplier of 2.0 is twice the average rate, and a multiplier of 0.5 is half the average rate.

Examples

Schumock et al. Drug Information Journal 2012

McConeghy et al. Pharmacotherapy 2016
Limitations to Spontaneous Reports

- Under-reporting
- Quality of reporting
- Reporting bias
  - Notoriety bias
  - Weber effect
  - Class effect
- Cannot determine rate (no denominator)
- Cannot be used to prove causality
Patient-Level Data (EHR or Claims)

• Surveillance using “big data” Determine rate of event

• FDA Sentinel Initiative
  – Active versus passive surveillance
  – Enables secure access to electronic health care data (such as health insurance claims and electronic health records)
  – To monitor the safety of FDA-regulated drugs and other medical products.
  – Involves over 50 organizations
    • Data partners (health care provider, insurance companies)
    • Academic partners (university and other research groups)
FDA Sentinel Initiative
**Figure 1. External linkage method for algorithm validation.**

Social Media to Identify Signals

• Identify previously unreported ADEs/side effects based on postings to social media sites.
• Uses natural language/semantic processing and complex ontologies.
STEP 3: Risk Evaluation and Confirmation

• Evaluate and confirm identified potential risks

• Pharmacoepidemiologic studies can quantify medication risks
  – Case-control studies – determine possible causes of a single disease
  – Cohort studies – determine possible outcomes of a single exposure
Cohort Type Studies

Exposed

Non-Exposed

Compare Incidence

Compare Prior Exposures

Diseased

Non-Diseased

Case-Control Studies
Pharmacoepidemiology Studies

• Prospective (registry data) or retrospective (using insurance claims or electronic medical record data) studies.
• Not randomized, “observational”.
• Significant efforts in analytic methods to control of confounding.
• Able to determine association between drug and event (not necessarily causality)
Figure 3. Adjusted risk of mortality (■), chronic obstructive pulmonary disease (COPD) exacerbations (◆), and hospitalizations (●) during follow-up in each regimen with theophylline compared with the regimen without theophylline. Point estimates represent hazard ratio for mortality and rate ratio for hospitalizations and exacerbations. Lines represent 95% confidence intervals.
STEP 4: Risk Prioritization
Risk Prioritization

• How do we weigh the potential risk against known benefits of the drug?
• From which perspective should we do this?
• What threshold should we use to act?
• What actions should we take?
• Are there potential negative consequences of the actions we take?
FDA evaluates benefits/risks for the population.

Provider evaluates benefits/risks for a patient.

Patient evaluates benefits/risks in terms of personal values.
Risk Prioritization Criteria (US FDA)

• Hazard assessment
  – Seriousness of the event (e.g., severity and reversibility)
  – Size the population exposed
  – Frequency of harm to those exposed

• Modulating factors
  – Context of drug’s use
    • Availability of and risk profiles of alternatives
    • Risk posed to vulnerable populations/subgroups
    • Clinical setting in which the drug is used
  – Quality of the data suggesting the risk
  – Biologic plausibility

• (Considered a priority by other groups*)

*US National Institutes of Health, European Medicines Agency, or World Health Organization.
Constantly Changing Equation
STEP 5: Risk Management

- Risk management involves *risk minimization* and *risk communication*.
  - Voluntary versus required of manufacturer by FDA.
  - Ranges from communication of risk, to required additional study (registry or active surveillance), to restricted distribution.
  - Risk Evaluation and Mitigation Strategies (REMS).
Example

Stakeholders
- FDA
- Drug Manufacturers
- Health Professionals (e.g., Physicians, Pharmacists, Nurses)
- Health Professional Students
- Patients

Risk Management Strategies & Education Training
- REMS, Medwatch, AERS
- Patient Safety and Evaluation of Drug Safety
- RCA, FMEA Reporting system: Local, institutional, National Continuing Education Workshops
- Curricular inclusion of courses: development of effective communication skills Medication/ Patient Safety Pharmacoepidemiology
- Gather information on drug -use

Future Research
- Ways to disseminate information and generate awareness on external reporting
- Consumer-Oriented Following Ethical Guidelines to improve quality of care
- Disclosure & information sharing with patients Standardization of practices to improve patient outcomes
- Socialization and effective communication New methods in determining errors Team -based approach
- Physician-Patient shared decision making

Stephanie Crawford
REMS – Risk Evaluation and Mitigation Strategies

• FDA requirement for specific medications to ensure benefit > risks
  – May be required for new products or products on the market with a newly identified risk

• REMS may include:
  – Medication guide/patient package insert
  – Communication plan
  – Elements to Assure Safe Use (ETASU)
  – Implementation System
## REMS Elements

<table>
<thead>
<tr>
<th>Name</th>
<th>Last Updated</th>
<th>Medication Guide</th>
<th>Communication Plan</th>
<th>ETASU</th>
<th>Implementation System</th>
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<tr>
<td>Adasuve (loxapine), aerosol, powder NDA #22549</td>
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<td><strong>Buprenorphine Transmucosal Products for Opioid Dependence (BTOD)</strong></td>
<td>10/04/2016</td>
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<td><strong>Shared System REMS</strong></td>
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</table>
REMS Example - iPLEDGE

• REMS program to prevent pregnancy while on isotretinoin
MEDICATION GUIDE
ZENATANE™ (ZEN – a – tän)
(isotretinoin capsules)

Read the Medication Guide that comes with Zenatane™ before you start taking it and each time you get a prescription. There may be new information. This information does not take the place of talking with your doctor about your medical condition or your treatment.

What is the most important information I should know about Zenatane™?
• Zenatane™ is used to treat a type of severe acne (nodular acne) that has not been helped by other treatments, including antibiotics.
• Because Zenatane™ can cause birth defects, Zenatane™ is only for patients who can understand and agree to carry out all of the instructions in the iPLEDGE Program.
• Zenatane™ may cause serious mental health problems.

1. Birth defects (deformed babies), loss of a baby before birth (miscarriage), death of the baby, and early (premature) births. Female patients who are pregnant or who plan to become pregnant must not take Zenatane™. Female patients must not get pregnant:
   • for 1 month before starting Zenatane™
   • while taking Zenatane™
   • for 1 month after stopping Zenatane™

If you get pregnant while taking Zenatane™, stop taking it right away and call your doctor. Doctors and patients should report all cases of pregnancy to:
• FDA MedWatch at 1-800-FDA-1088, and
• The iPLEDGE pregnancy registry at 1-866-495-0654

2. Serious mental health problems. Zenatane™ may cause:
• depression
• psychosis (seeing or hearing things that are not real)
• suicide. Some patients taking Zenatane™ have had thoughts about hurting themselves or putting an end to their own lives (suicidal thoughts). Some people tried to end their own lives. And some people have ended their own lives.
• Doctors must be registered and meet specific requirements each time they prescribe the drug.
• Pharmacies and distributors must be registered and meet specific requirements each time they dispense the drug. Limited quantity and pick-up time.
• Patients must be registered and sign informed consent.
iPLEDGE: Prescriber Enrollment
iPLEDGE: Patient Verification
**iPLEDGE ETASU**

**REGistered Patients**

- **Females of reproductive potential (FRP)**
  - **Before Treatment**
    - Sign a Patient Information/Informed Consent (for all patients) form for treatment
    - Sign a second Patient Information/Informed Consent About Birth Defects (for female patients who can get pregnant) form
    - Get a screening urine/blood pregnancy test
    - Receive patient ID card
    - Choose 2 effective forms of birth control
    - Start using the 2 forms of birth control simultaneously for at least 1 month
    - Get a second pregnancy test within the first 5 days of your menstrual period (patient with irregular cycle please check with your prescriber) in an approved lab
    - Access the iPLEDGE Program system to answer questions and to enter the 2 chosen forms of birth control. You can only answer your questions after your doctor has entered your test results into the iPLEDGE Program System
    - Get a prescription for a maximum 30-day supply

- **Male patients/Females of non-reproductive potential (FNRMP)**
  - **Before Treatment**
    - Sign a Patient Information/Informed Consent (for all patients) form for treatment
    - Receive patient ID card
    - Get a prescription for a maximum 30-day supply

**Each Month During Therapy**
iPLEDGE ETASU

**EACH MONTH DURING THERAPY**

- Use the 2 forms of birth control simultaneously
- See your doctor for a monthly pregnancy test in an approved lab
- Access* the iPLEDGE Program system to answer questions and confirm the 2 forms of birth control
- Get a prescription for a maximum 30-day supply
- Do not donate blood

**AFTER TREATMENT**

- Get a pregnancy test in an approved lab the last dose
- Continue to use the 2 forms of birth control simultaneously for 1 month after the last dose
- Do not donate blood for 1 month after the last dose
- Get a final pregnancy test 1 month after the last dose

- See your doctor to get a prescription
- Get a prescription for a maximum 30-day supply
- Do not donate blood

* Access to the iPLEDGE Program system is required to participate in the iPLEDGE program.
Risk Communication: From Regulatory Agencies

• Costa Rican Ministry of Health
  – Bulletins (Boletín de Farmacovigilancia)
  – Alerts (Alertas farmacovigilancia de seguridad)

• World Health Organization (WHO)
  – VigiBase® - global database of adverse drug reactions, obtain access here
  – SIGNAL Newsletter

• US FDA
  – MedWatch
  – Recall, market withdrawal, and safety alerts
  – www.fda.gov/Safety
Risk Communication: From Drug Manufacturers

- Product labeling/package insert
- “Dear Doctor” letters
- Patient medication guides
- Advertising
Risk Communication: Talking to Patients

• Remind patients there is always a balance between the risks and benefits of a medication.
• Be honest about the risk(s) in question.
• Assure patients that you and your staff will continue to do their best for them no matter what they choose.
• Listen to the patient.
Risk Communication: Talking to Patients

• Combine descriptive words (e.g. low risk) with numerical estimates.
  – Employ visual aids

• Use the same denominator.
  – E.g. 1 in 25 patients vs. 1 in 200 patients

• Use absolute numbers instead of relative risks.

• Present both positive and negative outcomes associated with the risk.
  – E.g. chances of survival and death
Risk Communication: Talking to Patients

“Why do I have to be a part of the iPLEDGE program?”
Conclusion

• At the time of drug approval there are potential adverse effects that are unknown because they were undetected in pre-marketing clinical studies.

• These can be serious, and will occur with widespread use.

• Post-marketing surveillance, or “pharmacovigilance,” is the means by which we identify those risks.

• Pharmacoepidemiology studies are used to more definitively evaluation/confirm the association between a drug and an adverse outcome.
Conclusion

• Both require the availability of large amounts of data.

• Healthcare practitioners need to do their part to report cases of suspected adverse drug events.

• Once known, we can manage (minimize and communicate) the risks of a drug.
Questions?