Conference on Pharmacovigilance and Drug Safety – A New Era

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Active Surveillance in Pharmacovigilance

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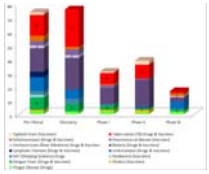
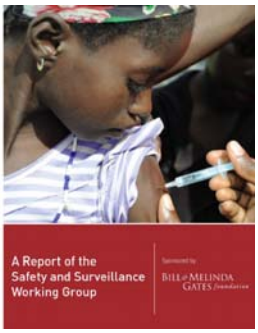
Why Pharmacovigilance?

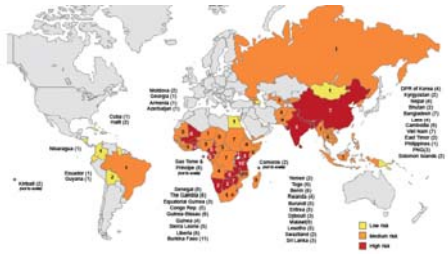
- Scale-up of medicine-centric public health programs
- Expanding new drugs and vaccines pipeline launched simultaneous or exclusively in low- and middle-income countries
- Much remains unknown about safety at drug or vaccine's approval, particularly among vulnerable, understudied populations
- Real or rumored adverse events can undermine public confidence
- Pharmacovigilance plans required or requested by regulatory agencies





- "Drugs and vaccines are reaching unprecedented numbers of people in low- and middle-income countries. These products have tremendous potential to save lives and reduce suffering, but many of the countries in which these products will be used do not have the capacity to effectively monitor their post-market safety."

Geographic Distribution of Projected New Product Launches



Report of the Safety Surveillance Working Group, 2014

Five Reasons for Active Surveillance Pharmacovigilance

1. Follow-up of safety signals
2. Investigate newer products that have a limited real-world safety profile
3. Calculate rates of and risk factors for adverse events
4. Complement other pharmacovigilance methods
5. Monitor pregnancy outcomes following prenatal drug exposure

1. Follow-Up of Safety Signals

- Follow-up of signals generated from preclinical studies, clinical trials, spontaneous adverse event reporting, relevant literature
- Can use retrospective and/or prospective study designs

Vaccine Safety Datalink Project

- Vaccine Safety Datalink (VSD) project, sponsored by the US CDC, conducts near–real-time, population-based, active surveillance for vaccine safety.
- Records of 9.2 million people annually from 8 health care systems in the US.
- Preselected outcomes based on data from pre-licensure trials, early reports from the Vaccine Adverse Event Reporting System (VAERS), literature on similar vaccines, and/or known biological properties of the vaccine or pathogen.

Vaccine Safety Datalink Project

- Detected one vaccine-safety problem with measles-mumps-rubella and varicella combination (MMRV) vaccine and seizures that led to a change in national vaccination policy.
- Nine other signals with various vaccines were fully investigated and ruled out.

Yih, et al. Pediatrics. 2011

Sentinel Initiative

- Improves US FDA's capability to identify and evaluate safety issues in near-real-time
- Enhances FDA's ability to evaluate safety issues not easily evaluated with the spontaneous reporting system
- Mini-Sentinel is a pilot project for developing and evaluating scientific methodologies that might later be used in a fully-operational Sentinel Initiative.
- Approximately 140 million individuals, claims & administrative data, 2000 - present (Mini-Sentinel)

www.mini-sentinel.org

From: **Rapid Assessment of Cardiovascular Risk Among Users of Smoking Cessation Drugs Within the US Food and Drug Administration's Mini-Sentinel Program**

JAMA Intern Med. 2013;():1-3. doi:10.1001/jamainternmed.2013.3004

Table. Results from the Rapid Assessment of Cardiovascular Risk and Use of Smoking Cessation Drugs in the Mini-Sentinel Program

Cohort[a]	No. of New Users	Follow-up, Person-years	No. of Outcome Events[b]	Incidence (95% CI) per 1000 Person-years	Incidence Rate (95% CI) per 1000 Person-years	Crude IRR (95% CI)	Adjusted IRR (95% CI)[c]
Analysis 1: Initiators of Therapy Who Had a Diagnosis of Tobacco Use Disorder[d]							
Varenicline	89 519	11 197	56	0.63 (0.47-0.81)	5.00 (3.78-6.50)	0.97 (0.69-1.35)	1.02 (0.71-1.47)
Bupropion	113 378	22 942	118	1.04 (0.86-1.24)	5.14 (4.26-6.16)	1 [Reference]	1 [Reference]
Analysis 2: Initiators of Therapy With Products Approved Specifically for Smoking Cessation[e]							
Varenicline	260 660	32 070	109	0.42 (0.34-0.51)	3.40 (2.79-4.10)	0.83 (0.37-2.31)	0.98 (0.43-2.23)
Bupropion	11 203	1462	6	0.54 (0.20-1.17)	4.10 (1.51-8.93)	1 [Reference]	1 [Reference]
Analysis 3: All Individuals Initiating Therapy							
Varenicline	260 660	32 070	109	0.42 (0.34-0.51)	3.40 (2.79-4.10)	1.58 (1.27-1.95)	1.52 (1.21-1.91)
Bupropion	745 004	209 478	452	0.61 (0.55-0.66)	2.16 (1.96-2.37)	1 [Reference]	1 [Reference]

- This rapid assessment found no consistent evidence of increased cardiovascular risk during the first treatment episode of varenicline among individuals with no recent diagnosis of cardiovascular events when compared with bupropion use.

Use of Automated Data Systems for Active Surveillance Pharmacovigilance

- Health maintenance organizations and health insurance plans
- US Medicaid, Medicare, Veterans Administration
- UK Clinical Practice Research Datalink (CPRD) (formerly General Practice Research Database)
- Netherlands PHARMO Record Linkage System

2. Investigate newer products that have a limited real-world safety profile

- Safety signals from pre-clinical studies and clinical trials
- Submitted to WHO and regulators as part of a risk management plan

Table 1 ASAQ Winthrop Risk Management Plan: issues to be documented

1. **Identified risks: to be minimized with specific information**
   - Intake during first trimester of pregnancy
   - Allergy
2. **Potential risks: to be quantified in large-scale studies**
   - Hepatotoxicity
   - Neutropenia/agranulocytosis
   - Somnolence
   - Audiometric dysfunction
   - Extra-pyramidal symptoms
   - Decreased efficacy (parasite resistance)
3. **Missing information: to be documented in new studies**
   - Safety of repeated administrations
   - Specific populations (HIV/AIDS patients,..)
   - Second and third trimester of pregnancy
   - Safety profile in non parasitaemic patients
   - Drug interactions & Interactions with traditional drugs and remedies
   - Efficacy in species other than *P. falciparum*

Bompart et al. Malaria Journal 2011, 10:143

- This Post-Authorization Safety Study (PASS) is intended to fulfill a regulatory post-marketing requirement to provide data regarding visual abilities in children taking azithromycin for acute pharyngitis/tonsillitis. The primary objective of the study is to examine the incidence of clinically significant worsening in any of the following ophthalmic exams: best corrected visual acuity (distance), color vision…. in a group of approximately 30 pediatric patients taking azithromycin oral solution.

3. Calculate rates of and risk factors for adverse events

- Cohort studies measure the incidence of adverse event(s) over a defined period of time in a selected population of individuals among groups of people whose exposure status differs
- Can be prospective or retrospective

A prospective study of highly active antiretroviral therapy in Indian human immunodeficiency virus positive patients

- Assess risk factors for ADRs to HAART
- 1,982 patients from ART center at hospital in Udipi.
- Risk factors: CD4+ T-cell counts; female; polypharmacy; opportunistic infections.

Records Linkage Retrospective Cohort Pharmacovigilance Study

Primary Aim:
To determine the incidence of and risk factors for anemia in adults on AZT-based HAART in Namibia

Secondary Aim:
To demonstrate the feasibility of using automated data bases and records linkage as a sustainable platform for assessing the safety and use of HAART to help support evidence-based decision-making

PHARMACOEPIDEMIOLOGY AND DRUG SAFETY (2011)
Published online in Wiley Online Library (wileyonlinelibrary.com) DOI: 10.1002/pds.2252

ORIGINAL REPORT

Records linkage of electronic databases for the assessment of adverse effects of antiretroviral therapy in sub-Saharan Africa

Catherine Corbett[1]*, Ishmael Katjitue[2], Assegid Mengistu[3], Francis Kalemeera[3], Evans Sagwa[4], David Mabirizi[4], Jennie Lates[3], Jude Nwokike[5], Sherrilyne Fuller[6] and Andy Stergachis[7,8]

EDT Exposure	MEDITECH Outcome	ePMS Additional risk factors
•HAART regimens, dispensing and substitution dates •Person name, date of birth, gender	• Hemoglobin values used to define anemia • Person name, date of birth, gender	•Clinical characteristics e.g., weight, CD4 count, WHO clinical stage. •Person name, date of birth, gender

Retrospective Cohort Studies Facilitated Through Records Linkage

- Use of administrative and clinical data bases
- Records linkage is commonly used in Western countries for pharmacovigilance
- Efficient and rapid studies are possible – provided that accurate and complete data are available

4. Complements Other Pharmacovigilance Methods

- Spontaneous reporting of adverse events has important strengths and limitations
- Active surveillance has performed better than spontaneous reporting
- While active surveillance can be more resource intensive, the use of sentinel sites for active surveillance and/or records linkage improves efficiency

Comparison of adverse drug events (ADE) detection systems used in the study

Group	Type of ADEs		Causality of ADEs		Severity of ADEs		Source of ADEs		
	Labelled	Unlabelled	Probable	Definite	Serious	Non-serious	Physician's notes	Nurse's notes	Patient interviews
Spontaneous reporting	2	5	7	Nil	5	2	7	Nil	Nil
Active surveillance	44* (85%)	8 (15%)	52	Nil	12* (23.1%)	40* (76.1%)	7 (13%)	12 (23%)	33 (64%)

Data are represented as the number of ADEs reported. *P<0.05 in comparison with spontaneous reporting.

Indian J Pharmacol | October 2006 | Vol 38 | Issue 5 | 363-364

- 7 adverse drug events were detected in 7 patients through the spontaneous reporting system, while 52 were detected in 37 patients through active surveillance

Components of Postmarketing Surveillance at US FDA

5. Monitor pregnancy outcomes following prenatal drug exposure

- Pregnancy exposure registry
- Prospective observational design that identifies pregnant women and actively collects information on drug exposures during pregnancy and associated pregnancy outcomes
- Pregnant women are enrolled as early as possible, based on exposure, before the outcome of the pregnancy is known

When are Pregnancy Exposure Registries Recommended?

- Drug is likely to be used during pregnancy
- Drug has suspected risks, based on toxicology, SAR, pharmacology, case reports
- When there is a need to provide margins of reassurance for risk-benefit, policy, guidelines
- Identify factors that affect risk of adverse outcomes
- Support change from assigned Pregnancy Category

FDA Guidance for Industry.
Establishing Pregnancy Exposure Registries. 2002

Antiretroviral Pregnancy Exposure Registry

– Provides early warning signal of major teratogenicity
– Estimates risk of major birth defects

Confidence intervals for prevalence of birth defects*—All prospective registry cases with follow-up data closed through January 31, 2006

	Overall
Number of live births	5560
Number if outcomes with at least one defect†	145 (2.6%)
95% Confidence intervals for prevalence‡ of birth defects§ for exposures in:	
First trimester	62/2117 (2.9%) 2.3%–3.7%
Second/third trimester	93/3443 (2.4%) 1.9%–3.0%
Any trimester	145/5560 (2.6%) 2.2%–3.1%
Risk of defects for first trimester exposures relative to second/ third trimester exposures	1.21 (0.88, 1.68)

Use of Artemisinin in Early Pregnancy

Active Surveillance: Sentinel Sites

- Institutions designated for data collection, such as hospitals, selected for their geographic location, medical specialty, and ability to diagnose accurately and report high quality data
- Advantages
  – Provides complete and more accurate data
  – Efficient
  – Ability to access medical records

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Active Surveillance in Pharmacovigilance

- Significant developments:
  - Use of databases
  - Sentinel sites
- Information contributes to:
  - Benefit-risk decision making
  - Treatment guidelines development/updating
  - Rational use of medicines
  - Improved patient safety

Disclaimer

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Thank You

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