Risk Interventions and their Evaluation: Two Case Studies

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Topics for Today's Discussion

- Types of Risk Intervention Programs
- Two Case Studies on Evaluation
  - Brief Review of the Labeling History
  - Overview of Risk Intervention Studies
  - Objective, Methods, Results and Conclusions
- Lessons Learned
- Future Directions

Risk Intervention Programs

- **Professional Labeling**
  - **Contraindications, precautions, warnings, and adverse events to caution on potential hazards**
  - **Black Box Warning is a labeling statement about serious events leading to significant injury and/or death**

Risk Intervention Programs

- **Types of Labeling**
  - **Professional Drug Label/Package Insert**
  - **Patient Package Insert is an extension of the labeling intended for distribution to patients with the drug in lay language**
  - ***Medication Guide is an information leaflet* required by regulation and distributed to patients with the drug to inform patients about the drug in lay language**

Risk Intervention Programs

- **Advertising**
  - **Voluntary restriction to journal type**
  - **Voluntary restriction of direct to consumer ads**
  - **Ads must present a brief, accurate and *balanced representation of diverse reactions*, contraindications, and effectiveness**
  - **Reminder ads that call attention to the name of the drug only are not permitted for drugs *with a Black Box Warning***

Risk Intervention Programs

- **Communications to health care practitioners and consumers**
  - **Dear Healthcare Practitioner letter & mailing by the sponsor**
  - **Press Releases and Talk Papers for the Press and posting in the FDA Website**
  - **Health Advisories to communicate serious health risks**

Risk Intervention Programs

- **Communications to health care practitioners and consumers**
  - **Educational Programs by sponsors directed to healthcare practitioners to ensure optimal prescribing and implementation of necessary precautions**
  - **Educational Programs by sponsors for the public/patients through toll free numbers, internet sites, newsletters, and collaborative efforts with patient advocacy groups**
  - **Sales force outreach**

Risk Intervention Programs

- **Packaging - Unit of Dose packaging used with patient package insert/med guide**
- **Restricted Distribution - Regulatory mechanism to ensure safer use and *availability of drug of benefit over* existing treatments to treat serious or life threatening conditions**
- ***Cessation of Marketing***
  - **Voluntary Withdrawal by the sponsor**
  - **Withdrawal of Approval/Imminent Hazard**

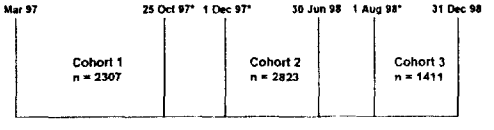
First Case History

- Approved in January 1997
- Marketed in March 1997
- Seven months after marketing, first Acute Liver Failure death
- Several Re-labelings and Dear Healthcare Practitioner letters including recommendations for Liver Transaminase testing

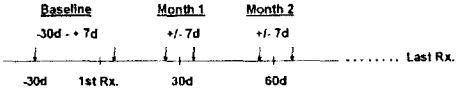
Study Objective

- To assess the impact of the labeling changes regarding liver transaminase (LT) monitoring in a large managed care organization (IPA) automated claims database (ICD-9 and CPT codes)
- Recommended LT monitoring varied slightly with each labeling change
- Last labeling change recommended a baseline test with monthly monitoring for first 8 months, data presented to AC 3/99

Overview of Study in the United HealthGroup Database



Study Method for Measuring Liver Transaminase Monitoring in UHG



Sample Size of Study Population, UHG

Ever received drug	9,369
Total person-years	4,873
≥ 90 day prior enrollment	7,568
Included in LT monitoring study	6,541

Liver Transaminase Monitoring at Baseline after the First Prescription by Time Period

	% with Baseline Test
Cohort 1 (n=2307)	24.5
Cohort 2 (n=2823)	37.0
Cohort 3 (n=1411)	45.1

Full Compliance with Monthly Liver Transaminase Monitoring (+/-7d) by Cohort among Drug users

	Month*					
	1	2	3	4	5	6
Cohort 1	2.6	0.8	0.3	0	0	0
Cohort 2	7.3	2.5	1.0	0.7	0.6	0.8
Cohort 3	9.3	4.2	2.7	0.5		

*Data Shown as Percentage of Eligible Subjects at Each Time Period

Conclusion

- Poor compliance with full LT monitoring scheme recommended by labeling
- Better compliance with baseline LT testing that improved with each labeling change to a maximum of 45%

Investigators

FDA	UHG
Dave Graham MD, MPH	Carol Drinkard, PhD
Evelyn M Rodriguez MD, MPH	Deborah Shatin, PhD

Second Drug History

- Approved in July 1993
- First reports of Ventricular Arrhythmia with an antifungal drug 12/94
- Two Dear Healthcare Practitioner letters that described new contraindications and warnings for specific drugs and conditions

Second Case History

- Black Box Warning with Contraindication for QT interval prolonging drugs and Cardiovascular and Medical Conditions, 2nd line indication & DHPL 6/98
- Unit of Dose packaging, Medication guide, & DHPL 11/98

Study Objective

- To describe the impact of the cumulative labeling changes through 6/98
  - CYP P450 3A4 Enzyme Inhibitor Drugs
  - QT Prolonging Drugs
  - Contraindicated Comorbidities

Methods

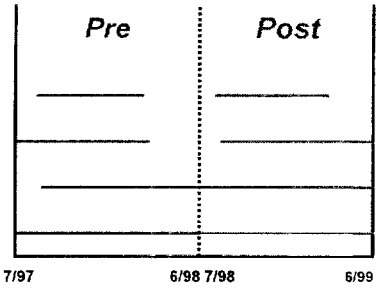
- Automated Databases: Sites A, B, and C
- Files
  - Enrollment : Cohort eligible
  - Pharmacy : Rxs
  - Inpatient & Outpatient : Comorbidity
- Time Periods
  - Before: 7/97 - 6/98
  - After: 7/98 - 6/99

Study Sites

	Model	*N, Millions*
A	IPA	3.2
B	Medicaid Managed	1.4
C	HMO	2.2

N based on calendar 1998, no material change for any of databases in 1999.

Cohorts



Pre and post cohorts included persons with any cisapride use in that study period
Zero time (t$_0$) date first dispensed prescription in study period

Cohorts

Site	Pre *N*	Post *N*
A	16,934	15,088
B	4,823	4,924
C	8,271	7,508

Contra-indicated Drugs

	Pre (%)	Post (%)
Site A: Any	14.4	12.6
P450 3A4	7.4	5.5
QT-Label	4.0	4.1
QT-Class	8.1	7.9
Site B: Any	33.8	33.6
P450 3A4	10.4	9.8
QT-Label	11.4	12.0
QT-Class	26.5	26.4
Site C: Any	18.3	16.1
P450 3A4	9.3	7.5
QT-Label	5.4	5.2
QT-Class	10.4	9.7

Contraindicated Comorbidity

Site	Pre	Post
	%	
A	14.9	14.0
B	41.3	38.8
C	15.3	14.5

Based on (pre/post) persons with 180+ days of enrollment: Site A: 13613/12418; B: 4379/4229; C: 6848/5812

Contraindicated Drug or Disease

Site	Pre	Post
	% of Cohort	
A	29.4	26.6
B	59.7	57.5
C	29.6	27.5

Conclusion

- No reduction in contraindicated use was found following the labeling change & DHPL of 6/98
- Patients frequently took contraindicated drugs or have contraindicated comorbidity and may be more frequent among the elderly (data not shown)

Study Group

FDA Investigators

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United Health Group (Site A)

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Harvard Consortium (Site C)

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Lessons Learned

- Labeling fatigue phenomenon
- Are special populations (elderly, others) at high risk when monitoring programs are suggested in labeling?
- How can reception, retention, and prescribing patterns be altered beyond those stimulated by labeling and DHPL?

Future Directions

- Conduct risk intervention studies in multiple automated databases that reflect the range of health care services delivery systems
- Validate the findings in automated databases with medical record review
- Conduct studies among prescribers to identify the "best communication practices" that will enhance timely and useful communication by industry and FDA

Future Directions

- Determine
  - How prescribers currently use information from Dear Healthcare Practitioner Letters and how this is translated into practice; does it vary by population?

Future Directions

- Determine
  - The kind of information that is most useful e.g., laboratory monitoring, contraindications (how many are too many?)
  - The impact of multiple labeling changes for a drug product

Future Directions

- Assess the impact of the health care services delivery system on prescribing and medical practice in the context of safer drug use
- Form industry-government partnerships (CRADAS) and interagency collaborations to conduct further studies to identify effective risk intervention strategies
- Using the results from these studies, implement strategies and evaluate success