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Improving Drug Safety: A Systems Approach

- Introduction
- Current System
- Limitations of Current System
- Proposal for the Future
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Improving Drug Safety: A Systems Approach

• “A desire to take medications is, perhaps, the greatest feature which distinguishes man from other animals.”

Sir William Osler, 1891
Improving Drug Safety: A Systems Approach

“If the whole materia medica, as now used, could be sunk to the bottom of the sea, it would be all the better for mankind, and all the worse for the fishes.”

Oliver Wendell Holmes
Medical Essays, “Comments and Counter-Currents in Medical Science"
Patient Safety and Medical Errors

• Iatrogenic injuries: up to 180,000 US deaths each year, and disability or prolongation of hospital stay in another 1.3 million

• Medical errors: 44,000-98,000 annual deaths, more than MVA, breast cancer, or HIV

• Medical errors: annual costs of $17-29 billion
Risks Associated With the Use of Drugs

• Adverse drug events are the most common iatrogenic causes of patient injuries
Improving Drug Safety: A Systems Approach

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Phases of Drug Development

PC: Preclinical studies
1: Dose escalation in normals
2: Dose ranging, first time in patients
3: Pivotal trials for registration
4: Post-marketing, not always required
Data Sources for Pharmacoepidemiology Studies

- Spontaneous case reports of adverse reactions
- Aggregate population-based data sources
- Computerized collections of data from organized medical care programs
- Data collected for pharmacoepi on an ongoing basis
- Existing data collected as part of other ad hoc studies
- Data collected de novo
Spontaneous Case Reports of Adverse Reactions

- Relied on for hypothesis generation
- A 1950s era system, which has been computerized
- AERS for drugs, or VAERS for vaccines
- The plural of “anecdote” is not “data”
Computerized Collections of Billing Data: Sources of Data

- Provider: Pharmacy
- Provider: Hospital
- Provider: Physician
- Payor
- Data User
Adverse drug events are the most common iatrogenic causes of patient injuries. Most are the result of an exaggerated but otherwise usual pharmacological effect of the drug. Yet, historically these have been ignored by pharmacoepidemiology, as they do not represent a focus of commercial and regulatory interest.
"Less than one in ten thousand—something like one in fourteen thousand—gets these side effects. Hardly anybody gets these side effects. They're extremely rare. You should be very proud."
Do you remember which symptoms you began with, and which are side effects?
"Of course, with any prescription drug, there are side effects..."
Drug Use and Effects Program

- Adverse drug reaction reporting
- Drug usage evaluation
- Pharmacy cost containment
Increasing Use of IT Interventions

- Immediate EPIC alerts with withdrawal of trimethobenzamide, pergolide, tegaserod, rofecoxib, and valdecoxib
- EPIC-delivered warnings regarding celecoxib, metoclopramide, rosuvastatin
IT Interventions/Evaluations Underway

- Metoclopramide RCT
- Warning fatigue
- Warfarin + NSAID RCT
- Insomnia/hypnotic RCT
- Warfarin + TMS RCT
Possible Future Interventions

- ACEIs and lipid lowering in diabetics
- Anticoagulation in AF
- Anti-rejection therapy in transplant patients
- Beta-blocker and aspirin use post-MI
- Drug selection in hypertensives
- Drug use in CHF
- Osteoporosis prophylaxis
CERTs Structure

FDA

AHRQ

Steering Committee

Public/Private Partnership

Nominating Committee

Educational Consortium

Committees

Iowa

Rutgers

Coordinating Center

Cornell

Duke

UNC

UAB

HMO Research Network

Centers

Houston

Arizona

Penn

Vanderbilt

Rutgers

Coordinating Center

Cornell

Duke

UNC

UAB

HMO Research Network

Centers

Houston

Arizona

Penn

Vanderbilt
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Limitations of Pre-marketing Trials-1

- Carefully selected subjects may not reflect real-life patients in whom drug will be used
- Study subjects may receive better care than real-life patients
- Short duration of treatment
- No info on comparative effectiveness
Limitations of Pre-marketing Trials-2

- Development costs lead to need for immediate huge sales ("blockbuster drugs"), and aggressive marketing practices.
- Yet, development programs with 3000 patients cannot reliably detect adverse events with an incidence of < 1 per 1000, even if severe.
Resulting Opportunities

- 51% of drugs have label changes due to major safety issues discovered after marketing
- 20% of drugs get new “black box” warnings after marketing
- 4% of drugs are ultimately withdrawn for safety reasons
Other Issues in Current System

- No incentive for sponsor to complete promised post-marketing safety studies
- DTC ads lead to over-use of the drug by patients for whom use of the drug is not compelling
Net Effect

• Public misunderstands “safety”: post-marketing discovery of a drug ADR means someone “messed up”
• Increasing concern about the safety of our drugs
• Over-reaction leads to increased pre-marketing requirements with delayed access and drugs dropped from development
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Risk Management

“Systematic information-sharing or actions undertaken to improve the balance of a drug product’s benefit(s) relative to its risk(s)”

Broad categories
  – Informational interventions
  – Active or administrative programs
Risk Management Tools: Informational

- Product labeling
- Patient informational materials
  - Medication guides
  - Patient package inserts
- Targeted health care provider education
Risk Management Tools: Active Intervention

- Constrain patient use
- Constrain health care prescribing or dispensing
- Restrict manner of product distribution
- Withdraw marketing status
  - IND access
  - Complete market withdrawal
Many Drugs With Risk Management Plans

- abacavir
- alosetron
- bosentan
- clozapine
- doxetilide
- felbamate
- fentanyl
- isotretinoin
- mifepristone
- pemoline
- sodium oxybate
- thalidomide
- tolcapone
QuickTime™ and a TIFF (Uncompressed) decompressor are needed to see this picture.
Evolution of Therapeutics

Empiric Choice of Therapy

Statistical Predictive Models of Patients Likely to Benefit or Suffer Harm

Personalized Medicine
Evolution of Therapeutics

Empiric Choice of Therapy

Statistical Predictive Models of Patients Likely to Benefit or Suffer Harm

RiskMAPS

Personalized Medicine
Risk Minimization Action Plans (RiskMAPs)

- RiskMAPs are key potential contributors to the public’s health
- The goal of RiskMAPs is to improve the risk/benefit balance of drugs
- Like any intervention, RiskMAPs should be evaluated for their safety and effectiveness
- The use of RiskMAPs is consistent with the trends underway in the nation’s health system, to improve patient safety

RiskMAPs are a logical next step toward the eventual goal of personalized medicine
“Decisions usually involve risk.”