Dangerous drugs and the genetic causes of disease

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Introduction

• Disclosures
  – No industry support
  – Served as expert witness on cerivastatin

• Two largely unrelated topics
  – Writing about dangerous drugs
    • Cerivastatin and rofecoxib
  – Creating consortium to conduct genome-wide association studies
  – First a brief scientific survey
Brief survey

• Which is a more serious breach?
  – Concealing the mortality risk of a drug
  – Serving as a “guest” author on a paper

• Which event is more newsworthy?
  – Concealing the mortality risk of a drug
  – Serving as a “guest” author on a paper
Baycol (cerivastatin)

• Cholesterol-lipid lowering “statin” drug
  – 6th statin, first marketed in Feb 1998
  – “Class” label for rhabdomyolysis
  – After first case, no further FDA monitoring
  – Withdrawn in August 2001

• Other statins extensively evaluated in large long-term trials
  – Prevention of heart attacks and strokes
  – Large increase in sales for all statins

Background

• Kefauver-Harris Amendments, 1962
  – Pre-market evaluation of efficacy and safety
  – Improved evaluation, slowed approval
  – No provision for post-market evaluation

• Prescription Drug Fee Users Act, 1992
  – Increased resources for rapid approvals
  – None for safety, 1992-2002
  – Congressional trust in sponsors’ self-interest
  – America as new drug safety testing ground

Steenburg C. Food Drug Law J 2006; 61: 295-384
Adverse event reporting system

- Voluntary reporting of adverse events
  - An incomplete case series of uncertain validity, the weakest form of evidence
  - Useful for rare AEs unrelated to drug indication, but not for common AEs
- FDA focus on new “unlabeled” AEs
- Main source of post-market safety information
### Rhabdomyolysis and Similar Reports

<table>
<thead>
<tr>
<th>Control No.</th>
<th>Age, Sex State</th>
<th>Complaint Terms</th>
<th>CPK Value</th>
<th>Fibrate Comed.</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>M98-167</td>
<td>Adult, M CA</td>
<td>Rhabdomyolysis, Renal failure, Incr. LFTs</td>
<td>Not reported</td>
<td>Lopid</td>
<td>Tx duration N/R. Incomplete follow-up.</td>
</tr>
<tr>
<td>M98-217</td>
<td>Adult, F AL</td>
<td>Rhabdomyolysis, Renal failure, Generalized myalgia, Leg pain</td>
<td>&gt;20,000</td>
<td>Lopid</td>
<td>Tx dur. 3-4 wks. Dialysis. Hospitalized. Improving.</td>
</tr>
<tr>
<td>M98-177</td>
<td>64, F PA</td>
<td>Hepatitis, Incr CPK, Muscle &amp; back pain/ weakness, Body aches, Headache</td>
<td>27,640</td>
<td>No</td>
<td>Tx duration 28d. Debilitating. Improved</td>
</tr>
<tr>
<td>DE 979005</td>
<td>70, F SD</td>
<td>Myopathy, Rhabdomyolysis Complaints: multiple myalgia, muscular soreness</td>
<td>3,180</td>
<td>Gemfibrozil</td>
<td>Tx duration 20 d. Forced diuresis No indication for virus infection Reversible</td>
</tr>
<tr>
<td>D97-008</td>
<td>67, F JMM</td>
<td>Creatine PK increase</td>
<td>17,220</td>
<td>Gemfibrozil</td>
<td>Tx duration 98 d. Hepatitis A. Life-threatening Resolved</td>
</tr>
</tbody>
</table>

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**Haltom vs Bayer Corp, Plaintiff's Exhibit 211.**
Pharmacokinetic study

• 3 day cross-over study of 10 patients of 0.3 mg Baycol with or without gemfibrozil
  – Area under the concentration-time curve increased by 559% (range, 138 to 995%)
  – Dose of 0.3 equivalent to 1.7 mg

• Gemfibrozil contraindication letter not submitted to the FDA until Dec 1999
  – Leisurely approach as public-health hazard

Protective order, item #19

“This Order shall not prevent any persons bound hereby from making use of information or documents without the restrictions of this Order if the information or documents are lawfully in their possession and/or lawfully obtained ... and not designated ‘Confidential’ or subject to a protective order.”
Methods for a paper

• Nueces County Clerk provided public trial exhibits for $1 per page (novel data)
• Sought co-authors, discussed with plaintiffs’ attorneys, UW deans and chairs and UW attorneys general
• Multiple reviews from 4 scientists, Bayer, JAMA editors and attorneys

## Reports through May 2000

<table>
<thead>
<tr>
<th>Confirmed cases of Rhabdomyolysis</th>
<th>Atorvastatin (^1)</th>
<th>Cerivastatin (^1)</th>
<th>Gemfibrozil (^1)</th>
<th>Report Rate /100,000 Prescr.</th>
<th>Report Rate /1000 Prescr.</th>
<th>Report Rate: Ceriva vs. Atorva</th>
</tr>
</thead>
<tbody>
<tr>
<td>with concomitant Gemfibrozil (^2)</td>
<td>1</td>
<td>66</td>
<td></td>
<td>0.003</td>
<td>2.896</td>
<td>855</td>
</tr>
<tr>
<td>with concomitant other fibrates</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>with concomitant Cerivastatin</td>
<td></td>
<td></td>
<td>65</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>with concomitant other statins</td>
<td>1</td>
<td>3</td>
<td>5</td>
<td>0.003</td>
<td>0.131</td>
<td>39</td>
</tr>
<tr>
<td>with no concomitant fibrates or</td>
<td>16</td>
<td>23</td>
<td>3</td>
<td>0.054</td>
<td>1.093</td>
<td>20</td>
</tr>
<tr>
<td>Total</td>
<td>18</td>
<td>84</td>
<td>73</td>
<td>0.061</td>
<td>4.110</td>
<td>68</td>
</tr>
</tbody>
</table>

\(^1\) primary or secondary suspected

\(^2\) Cerivastatin with concomitant Gemfibrozil: 1 case was found under concomitant medication in addition explaining the difference of Gemfibrozil with concomitant Cerivastatin
“The findings indicate that in patients receiving monotherapy, cerivastatin substantially elevates risk for rhabdomyolysis compared with other statins. In combination with gemfibrozil, cerivastatin patients were also found to be at a remarkable disadvantage compared with patients receiving gemfibrozil with another statin.”

Haltom vs Bayer Corp, Plaintiff’s Exhibit 515.
“On August 2, 2000, senior members of Bayer’s Global Drug Safety team and consultants met with Plischke to discuss the accumulation of adverse event reports. A consensus emerged that the data concerning Baycol’s dangers ‘was putting the brand at risk.’ When that conclusion was communicated to Ebsworth, he dismissed the reservations of the safety experts and instructed his marketing team ‘to promote the hell out of this product.’”

--William H. Pauley III, District Judge, 03-Civ-1546

Ideology of deregulation

“Those of us who have looked to the self-interest of lending institutions to protect share holder equity, myself included, are in a state of shocked disbelief…. Yes, I’ve found a flaw. I don’t know how significant or permanent it is. But I’ve been distressed by the fact.” --Alan Greenspan

NY Times, Oct 24, 2008
Vioxx (rofecoxib)

• NSAID for arthritis and pain
• No more pain relief than other NSAIDs
• Supposed to have fewer GI side effects
• Approved in 1999, advertised heavily
• About $3 billion per year in sales
• Withdrawn 2004 due to heart attack risk
Placebo controlled trials

• Studies of prevention of colon polyps
  – Effort to gain approval for new indication
  – Identified heart attack risk

• Studies of prevention of cognitive decline
  – Another effort for a new indication
  – In published reports, Vioxx “well tolerated”
  – Internal analyses made public by litigation but not submitted to FDA in timely fashion
  – Another opportunity for drug-safety paper

Approve Trial, final results. Lancet 2008; 372: 1756-64
### Mortality in Alzheimers trials

Intention to treat analyses conducted by the sponsor in April 2001

<table>
<thead>
<tr>
<th>Trial</th>
<th>RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>091</td>
<td>4.4</td>
<td>1.2-16</td>
</tr>
<tr>
<td>078</td>
<td>2.6</td>
<td>1.2-5.6</td>
</tr>
<tr>
<td>Both</td>
<td>3.0</td>
<td>1.6-5.8</td>
</tr>
</tbody>
</table>

FDA review of safety report

• Safety report to FDA in July 2001 included only on treatment deaths

“Please clarify whether the safety monitoring board and the IRB overseeing these studies are aware of the excess total cause mortality.... Have they commented on the ethics of continuing 078 in light of the mortality data?” (FDA, December 2001)
Sponsor’s reply

Mortality findings are “small numeric differences … most consistent with chance fluctuations…. There is no data safety monitoring board. MRL has not provided these data to the individual IRBs because MRL does not believe that a safety issue has been identified…. In the absence of a clear and compelling safety issue, MRL has not broken the study blind…”
Rofecoxib Alzheimer trials

• Intention to treat analyses of two trials showed increase in total mortality
  – A finding and a replication
  – No DSMB to protect patients
  – ITT data not submitted to FDA until 2003

• ITT analyses and data not made public or submitted to FDA in a timely fashion
  – Public health hazard of concealed risk

Celecoxib in Alzheimer’s

• RCT of 425 patients, 200 bid vs placebo, completed in 1999

• RR of CV events = 3.3 (0.99 to 10.8)

• Results available in 2000
  – Not submitted to FDA until June 2001
  – Never published
  – Not “released” until Jan 2005

Summary: Vioxx

• An approved drug with CV and mortality risks identified or made public late

• Some safety issues concealed

• Magnitude of harm to public related to
  – Rapid early expansion of use by DTCA
  – Late identification of risks
  – Willingness of physicians to use new drug
Vioxx trials and authorship

• Many trial reports and reviews ghost authored by company employees
  – Academic authors paid as “guest” authors

• Three “guest” authors for study 078
  – Probably never saw the internal company analyses showing increased mortality

• Unscientific observation: the guest authorship attracted media attention

The Greenspan problem

- Asymmetric interest in efficacy and safety
  - Fiduciary duty to shareholders for return
  - Parent-like relationship to new-born product

- Failed assumption of rational drug makers
  - Safety problems as impediment to marketing success
  - Conflict of interest to expect marketing teams to address safety issues in post-approval setting
  - Creation of a distorted knowledge base
  - Public health as competing interest
  - Need for disinterested independent regulation

Brief survey

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  – Concealing the mortality risk of a drug
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  – Serving as a “guest” author (on a paper that conceals a mortality risk)
CHARGE consortium

• Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE)
• Genome-wide association studies
• Design of CHARGE Consortium
  – Selected findings
• Epidemiological and public-health observations
Genome-wide association studies

• Unbiased mapping effort to identify loci
• Search takes advantage of haplotype block structure of human genome
• Technology allows relatively “low-cost” studies in unrelated individuals
• Agnostic approach to biology sometimes leads to new biology
Cardiovascular Health Study

- Cohort study of 5888 older adults recruited at 4 US sites in 1989-90
  - Multiple measures over time

- GWAS data in participants free of clinical CVD at baseline (n = 4056)
  - Primary aim: MI, stroke, and HF
  - Assumed effect sizes all > 1.5
  - Secondary: all other phenotypes
Published Genome-Wide Associations through 6/2009
439 published GWA at p ≤ 5 x 10^{-8}

www.genome.gov/GWAStudies
Power for binary outcome

MAF = 0.2; RR = 1.2

- alpha = 1E-6
- alpha = 5E-7
- alpha = 5E-8

MAF = 0.2; RR = 1.3

n cases, (1:1 matching)
Origins and goals of CHARGE

• Side effect of GWAS technology
  – Need for large samples and replication

• Voluntary federation of 5 complex cohort studies, each with its own organization
  – Simple organizational structure

• Conduct of prospective meta-analyses across multiple common phenotypes

CHARGE eligibility and cohorts

• CVD/Aging cohorts with GWAS data
  – CHS, FHS, ARIC, AGES, Rotterdam
  – Study design as organizing principle

• Population-based cohort studies
  – Similar data collection methods
  – Multiple measures over time
  – Long-term follow-up of events
  – Total sample size more than 40,000
Analysis

• Within-study, additive genetic model
  – Count of alleles or estimated dosage
  – Simple, repeated 2.5 million times
  – Robust and readily interpretable
  – Local analysis by local experts

• Between-cohort meta-analysis of results
  – Share results not individual level data
  – More powerful than 2-stage design
  – Culturally powerful for collaboration

Skol AD. Nat Genet 2006; 38  209-213
CHARGE working groups

- CHS origins of working-group model
- Decide on and harmonize phenotypes
  - Develop plans/paper proposals
  - Adapt the “central” analysis plan
  - Agree on timing for data sharing
  - Establish responsibilities & author lists
  - Plan for follow-up genotyping
  - Decide on other collaborations
QT interval duration

Figure 1 QT interval association results for 2,543,686 imputed SNPs in 13,685 individuals from three cohorts. Results are shown on the $-\log_{10}(P)$ scale and are truncated at $-\log_{10}(P) = 18$ for display purposes. The solid bar corresponds to the genome-wide significance threshold of $5 \times 10^{-8}$.
Example: QT interval duration

- Nine of 14 loci in genes known to be associated with myocardial repolarization

- Five novel loci
  - 16q21 near NDRG4 and GINS3
  - Near PLN, inhibitor of SR Ca^{+2} ATPase
  - 3 loci (1p36.31, 16p13.3, 17q12) with less obviously plausible explanations

Newton-Cheh C. Nat Genet 2009; 41: 399-406
Blood pressure findings

• 29136 subjects from CHARGE cohorts
• A rare variant in CYP17A1 associated with Mendelian forms of hypertension
• ATP2B1 encodes a membrane Ca+2 dependent ATPase in endothelium
• Variant in SH2B3 also associated with diabetes and celiac disease

Blood Pressure: Gene Scores

Blood pressure: next steps

• Meta-analysis of full CHARGE and Global BPGen results, n = 64,773

• Type SNPs in an experiment involving many other Europeans, n = 50,000

• Take results into additional populations and ethnicities

## Selected CHARGE results

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Loci, N</th>
<th>Journal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uric acid</td>
<td>3</td>
<td>Lancet 2008;372:1953</td>
</tr>
<tr>
<td>ECG QT interval</td>
<td>5</td>
<td>Nat Genet 2009;41:399</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>10</td>
<td>Nat Genet 2009; 41: 677</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>3</td>
<td>Circ CV Genet 2009:2:125</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>1</td>
<td>Hum Mol Genet 2009;18:2700</td>
</tr>
<tr>
<td>Menarche</td>
<td>2</td>
<td>Nat Genet 2009;41:648</td>
</tr>
<tr>
<td>Renal function</td>
<td>3</td>
<td>Nat Genet 2009;41:712</td>
</tr>
<tr>
<td>Waist circumference</td>
<td>1</td>
<td>PLOS Gen 2009;5:e1000539</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>1</td>
<td>Nat Genet 2009; 41: 879</td>
</tr>
<tr>
<td>Echo traits</td>
<td>5</td>
<td>JAMA 2009; 302: 168</td>
</tr>
<tr>
<td>Red cell traits</td>
<td>23</td>
<td>Nat Genet 2009; Oct 11, 2009</td>
</tr>
<tr>
<td>Duffy antigen</td>
<td>-</td>
<td>Blood 2009; accepted</td>
</tr>
</tbody>
</table>

Selected challenges

• Maintaining communications, trust and transparency across CHARGE cohorts
• Managing work flow across 30 working groups with limited resources
• Identifying and coordinating additional genotyping efforts and collaborations
• Vast, complex, and exciting effort
Selected achievements

• Novel research structure and framework
  – Development of research resource
  – Many analyses ongoing and planned
  – Opportunities for “champions” to lead
  – Setting for “ancillary” studies
  – Catalyst for new studies of all kinds

• International mentorship
  – Prominent role for young investigators
  – Their talents, insights, and energy
Clinical translation

• Prediction
  – Diagnostic and prognostic
  – Limited discrimination

• Personalized medicine
  – Therapeutic optimization
  – EGRF mutations, tyrosine kinase inhibitors, and non-small cell lung cancer as example

• Novel biologic insights
  – Future targets, prevention or treatment

GWAS and CV epidemiology

• Two goals of epidemiology
  – Identification of causes of disease
  – Improvements in the health of the public

• Translational requirements
  – Valid and reliable test
  – Effective preventive measure available
  – Evidence of favorable risk-benefit profile
  – Cost-effective applications available
Population biology

- **Immediate benefit**
  - Novel loci and biological insights
  - New mechanisms and pathways

- **Little immediate translational benefit**
  - Population scientists contributing ideas to our basic science colleagues
  - Grand experiment in collaboration

Collaborators

• Drug safety
  – Alta Charo, Curt Furberg, Susan Heckbert, Thomas Koepsell, David Korn, Dick Kronmal, Lewis Kuller, Eric Larson, Thomas Lumley, Wayne Ray, Ken Rice, Frits Rosendaal, David Siscovick, Nick Smith, Russ Tracy, Jan Vandenbroucke, Noel Weiss, and Alastair Wood

• CHARGE consortium
  – Chris O’Donnell, Eric Boerwinkle, Villi Gudnason, Tammy Harris, Bert Hofman and many others