Pharmaceutical Industry Influence on Medical Practice and the Use of Drugs

Consumer Issues Conference: Pills, Potions, and Profits
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Overview
- Misprescribing/overprescribing of drugs
- Statistics on drug promotion expenditures by drug companies
- Advertising directed at physicians
- Off-label promotion
- Criminal and civil monetary penalties against the pharmaceutical industry
- Propublica’s Dollars for Docs
- Pharmaceutical companies influencing clinical practice guidelines

Misprescribing/Overprescribing of Drugs

Generating Drug Company Profits

Misprescribing/Overprescribing of Drugs

- Definitions:
  - Prescriptions that are either entirely unnecessary, unnecessarily dangerous, or unnecessarily expensive.
  - Prescriptions for which the risks outweigh the benefits, thus conferring a negative health impact on the patient.
  - More than 1.5 million people are hospitalized and 100,000 die each year from largely preventable adverse reactions to drugs that should not have been prescribed as they were in the first place.

www.uwyo.edu/consumerconference
Seven Deadly Sins of (Mis)Prescribing

• The disease for which the drug is prescribed is actually an adverse event to another drug.
• A drug is used to treat a problem that, although in some cases susceptible to a pharmaceutical solution, should first be treated with common-sense lifestyle changes.
• The medical problem is both self-limited and completely unresponsive to treatments, such as antibiotics, or does not merit treatment with certain drugs.
• A drug is the preferred treatment, but instead of the safest, most effective—and often least expensive—drug, a less preferable alternative is used.

Seven Deadly Sins of (Mis)Prescribing (cont.)

• Prescribing two drugs, each of which when used alone may be safe and effective, but together can cause serious injury or death.
• Two or more drugs in the same therapeutic category are used, the additional one(s) not adding to the effectiveness, but clearly increasing the risk to the patient.
• The right drug is prescribed, but the dose used is dangerously high.

Who is Responsible for the Misprescribing and Overprescribing of Drugs

• The drug industry
• Physicians
• The Food and Drug Administration
• Pharmacists
• Patients

Statistics on Drug Promotion Expenditures by Drug Companies

Spending on Drug Sales in the U.S.

Number of Prescriptions Sold in the U.S.
Drug Promotions Expenditures in the U.S.

- In 2004, estimated pharmaceutical marketing expenditures in the U.S. was $57.5 billion (24.4% of drug sales). (Assuming same percent in 2010, marketing expenditures would have been $75 billion.)
- In comparison, drug companies spend about 13.4% on research and development.


<table>
<thead>
<tr>
<th>Type of Promotion</th>
<th>Estimate (US$ Billion)</th>
<th>Percent of Total</th>
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</thead>
<tbody>
<tr>
<td>Samples</td>
<td>15.9</td>
<td>27.7</td>
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<tr>
<td>Detailing</td>
<td>20.4</td>
<td>35.5</td>
</tr>
<tr>
<td>DTC Ads</td>
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<td>7</td>
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<tr>
<td>Meetings</td>
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<td>3.5</td>
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<tr>
<td>Journal ads</td>
<td>0.5</td>
<td>0.9</td>
</tr>
<tr>
<td>Other</td>
<td>14.7</td>
<td>25.5</td>
</tr>
<tr>
<td>Total</td>
<td>57.5</td>
<td>100</td>
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</tbody>
</table>


Advertising to Physicians

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www.uwyo.edu/consumerconference
Advertising Defined

• “the science of arresting the human intelligence long enough to get money from it” (Definition of advertising by Canadian economist, Stephen Leacock. The Garden of Folly, 1924)

1996 Ad from an Advertising Agency to Marketing Departments of Drug Companies

Commentary Regarding Advertising Agency Ad

• In the April, 1996, issue of Lancet, William Douglas McAdams, Inc, not only invents a new concept in functional neuroanatomy—the hippocampus as “the prescription-writing center of the brain”—but also promises that “all our communications are focused on making the hippocampus respond positively to your product”. The firm does so through creative and educational programmes with “a unique medical discriminator—an innovative, medically relevant idea that makes your customer see (and remember) how your product is superior and unique.” Although recent research has linked abnormalities of the hippocampus to schizophrenia and post-traumatic stress disorder; this advertisement contains the first suggestion that they are also associated with misprescribing.... [emphasis added]

Ad from an Advertising Agency to Marketing Departments of Drug Companies

Commentary Regarding Advertising Agency Ad (cont)

• ...The poor prescribing of many physicians is surely influenced by drug industry spending on promotion. Perhaps the hippocampus mediates this drug-firm-induced disorder. The proposed pathophysiological mechanism of such commercially driven prescribing is well described in the advertisement: “[the hippocampus] processes information by connecting new concepts with the parts of the brain where gut instincts are formed, areas that influence emotional behavior and form memories”. [emphasis added]

You can call it the Catalyst specialty. Our proven approach reaches the specialists who are vital to your brand’s growth…and you success.

If you demand performance, we’ll show you how our experts can push the limits for your brand…..

**FDA Drug Advertising Enforcement 1997-2007**

**FDA Warning and Notice of Violation Letters to Drug Companies**

<table>
<thead>
<tr>
<th>Year</th>
<th>Letters</th>
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<tbody>
<tr>
<td>1997</td>
<td>140</td>
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<tr>
<td>1998</td>
<td>157</td>
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<td>1999</td>
<td>108</td>
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<td>2004</td>
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<td>2005</td>
<td>29</td>
</tr>
<tr>
<td>2006</td>
<td>22</td>
</tr>
<tr>
<td>2007</td>
<td>20</td>
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</table>

**Off-Label Promotion**

**Off-Label Promotion - Background**

- FDA-approved drug label: indications for use (diseases and patient groups) and doses.
- Physicians can prescribe any FDA-approved drug for purposes, patients, and doses outside those listed on the label (FDA does not regulate the practice of medicine).
- Drug companies are prohibited by the FDA from engaging in direct promotion of “off-label” use.

**Off-Label Promotion – Analysis of Strategies and Practices by Kesselheim et al. (1)**

- The researchers studied unsealed whistleblower complaints in “qui tam” cases filed against drug companies filed under the U.S. federal False Claims Act that involved allegations of off-label marketing.
- Time period studied: January 1996-October 2010
- The researchers conducted structured reviews of the complaints and coded and analyzed the strategic goals of each off-label marketing scheme and the practices used to achieve those goals, as reported by the whistleblowers.

PLOS Medicine, April 5, 2011
Off-Label Promotion – Analysis of Strategies and Practices by Kesselheim et al. (2)
- 41 complaints involving 18 cases settled for a total of $7.9 billion.
- Drug companies: Parke-Davis/Warner-Lambert, Serono, InterMune, Bristol-Myer-Squibb, Cell Therapeutics, Orphan Medical, Medicis, Cephalon, Eli Lilly, Pfizer, AstraZeneca, Ortho-McNeil-Jansen, Novartis (2), Forest, Allergan, Scios, Wyeth
- Whistleblowers (n=55):
  - Pharmaceutical sales representatives, 39 (71%)
  - Sales or accounting managers, 11 (20%)
  - Unaffiliated physicians, 5 (9%)

Off-Label Promotion – Analysis of Strategies and Practices by Kesselheim et al. (3)
- Identified 3 mutually exclusive off-label marketing strategies in the 41 complaints:
  - Expansion to unapproved disease entities, 35/41 (85%); e.g., gabapentin (Neurontin; Parke-Davis/Warner Lambert) approved for epilepsy, promoted for bipolar disorder/depression
  - Expansion to unapproved disease subtypes, 22/41 (54%); e.g., nesiritide (Natrecor; Scios) approved for acute decompensated CHF, promoted for chronic stable CHF
  - Expansion to unapproved doses, 14/41 (34%)

Off-Label Promotion – Analysis of Strategies and Practices by Kesselheim et al. (4)
- Identified 4 mutually exclusive categories of marketing practices in 41 complaints:
  - Prescriber-related, 41/41 (100%)*
  - Internal business-related, 37/41 (90%)*
  - Payer-related, 23/41 (56%)
  - Consumer-related, 18/41 (44%)

Off-Label Promotion – Analysis of Strategies and Practices by Kesselheim et al. (5)
- Prescriber-related practices were the centerpiece of the whistleblowers’ complaints:
  - Self-serving presentations of scientific literature given physicians false or unbalanced study data supporting an unapproved use: 31/41 (76%)
  - Encouraged off-label use via direct financial incentives (e.g., honoraria and gifts): 35/41 (85%)
  - Free samples to promote off-label use: 8/41 (20%)
  - CME seminars organized with speakers known to promote off-label use: 22/41 (54%)

Off-Label Promotion – Analysis of Strategies and Practices by Kesselheim et al. (6)
- Internal business-related practices: reported to be company-wide, rather than work of individual manager or group of managers:
  - Intramural meetings and seminars in which marketing practices were discussed: 27/37 (73%)
  - Development of brochures and other materials for dissemination: 17/37 (46%)
  - Often included specific efforts by the drug manufacturer to conceal the off-label marketing activities: 25/37 (68%)

Drug Detailing and Off-Label Promotion
Steinman et al. Study (1)
- Drug detailing: visits by pharmaceutical sales representatives to physician offices.
- Researchers analyzed data collected from physicians by a market research company about detail visits for gabapentin (Neurontin; Parke-Davis/Warner Lambert); obtained from documents subpoenaed in a qui tam whistleblower lawsuit alleging off-label promotion.
- Described characteristics and content of the detail visits for gabapentin and self-reported impact on future prescribing.
Drug Detailing and Off-Label Promotion
Steinman et al. Study (2)

• Reviewed 116 Detailing Reporting Forms completed by 97 physicians in 1995-1999 (91 from 1996)

PLOS Medicine, April 24, 2007

Drug Detailing and Off-Label Promotion
Steinman et al. Study (3)

• Individual or small group setting? (n=91)
  ➢ Individual: 88%
  ➢ Small group (2-3 physicians): 12%

• Time spend on detail? (n=107)
  ➢ < 5 minutes: 67%
  ➢ 6-10 minutes: 20%
  ➢ > 10 minutes: 13%

PLOS Medicine, April 24, 2007

Drug Detailing and Off-Label Promotion
Steinman et al. Study (4)

• Main messages of the detail? (n=115)
  ➢ Approved use (epilepsy, adjunctive or not specified): 46%
  ➢ Unapproved uses: 38%
    - Epilepsy monotherapy: 3%
    - Pain or neuropathy: 25%
    - Psychiatric conditions: 3%
    - Migraine: 1%
    - Other specified unapproved use: 4%
    - General mention of unapproved uses: 5%
    - Doses > 1,800 mg/day: 5%

PLOS Medicine, April 24, 2007

Drug Detailing and Off-Label Promotion
Steinman et al. Study (6)

• Intended future change in level of prescribing or recommendation (n=108):
  ➢ Increase: 46%
  ➢ Maintain: 54%
  ➢ Decrease: 0%

PLOS Medicine, April 24, 2007

Rapidly Increasing Criminal and Civil Monetary Penalties Against the Pharmaceutical Industry:
1991 to 2010

December 16, 2010

Sammy Almashat, M.D., M.P.H, Charles Preston, M.D., M.P.H, Timothy Waterman, B.S.,
Sidney Wolfe, M.D.
Public Citizen’s Health Research Group

Available at http://www.citizen.org/documents/rapidlyincreasingcriminalandcivilpenalties.pdf
Criminal and Civil Monetary Penalties Against the Pharmaceutical Industry - Background

- Illegal drug company activities have contributed to inflated spending on prescription drugs.
- Public Citizen's Health Research Group (HRG) examined trends from 1991 to November 2010 in federal and state criminal and civil actions against pharmaceutical companies. Compiled a database of all major (> $1 million) federal and state criminal and civil settlements finalized against drug companies.
- Laws being violated included False Claims Act (legal tool used to prosecute fraud against the government; enacted in 1863 during Civil War) and the Food Drug and Cosmetic Act which prohibits false therapeutic claims about a product, including off-label promotion.

Criminal and Civil Monetary Penalties Against the Pharmaceutical Industry - Overall Trends

- **Figure 1.** Number of Pharmaceutical Industry Settlements, 1991-2010
  - 165 settlements

Criminal and Civil Monetary Penalties Against the Pharmaceutical Industry - Worst Offenders

- **Table 2.** Pharmaceutical Company Penalties: Worst Offenders

<table>
<thead>
<tr>
<th>Company</th>
<th>Total Financial Penalties 1991-2010 ($ millions)</th>
<th>Percent of Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>GlaxoSmithKline</td>
<td>4501</td>
<td>22.7</td>
</tr>
<tr>
<td>Pfizer</td>
<td>2935</td>
<td>14.8</td>
</tr>
<tr>
<td>Eli Lilly</td>
<td>1712</td>
<td>8.6</td>
</tr>
<tr>
<td>Schering-Plough</td>
<td>1339</td>
<td>6.8</td>
</tr>
<tr>
<td>Bristol-Myers Squib</td>
<td>890</td>
<td>4.5</td>
</tr>
<tr>
<td>AstraZeneca</td>
<td>883</td>
<td>4.5</td>
</tr>
<tr>
<td>TAP Pharmaceutical</td>
<td>875</td>
<td>4.4</td>
</tr>
<tr>
<td>Merck</td>
<td>806</td>
<td>4.1</td>
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<tr>
<td>Serono</td>
<td>704</td>
<td>3.6</td>
</tr>
<tr>
<td>Purdue</td>
<td>620</td>
<td>3.1</td>
</tr>
</tbody>
</table>
Criminal and Civil Monetary Penalties Against the Pharmaceutical Industry – Types of Violations

Propublica’s Dollars for Docs

- For many, drug companies kept the names of their speakers -- and how much they paid them -- secret.
- Over the past two years, drug companies have begun posting this information on their web sites, some as the result of legal settlements with the federal government.
- ProPublica took these disclosures and assembled them into a single, comprehensive, searchable database.
- Federal law requires that all companies publicly report this data beginning in 2013. That information will be posted on a government web site.

Ornstein C, et al. ProPublica, 9/7/11

Propublica’s Dollars for Docs - Background (2)

- Only the 12 companies that have disclosed payments on their web sites are included. Their combined prescription drug sales amounted to about 40 percent of the U.S. market in 2010.
- The data does not include payments for speaking at CME courses, which are run independently from the pharmaceutical companies.

Ornstein C, et al. ProPublica, 9/7/11

http://projects.propublica.org/docdollars/
**Propublica’s Dollars for Docs**

**Companies Providing Information**

- Allergan
- AstraZeneca
- Cephalon
- Eli Lilly
- EMD Serono
- GlaxoSmithKline*
- Johnson & Johnson
- Merck*
- Novartis
- Pfizer
- Valeant
- ViiV*

*Posting voluntarily

Ornstein C, et al. Propublica, 9/7/11

**Propublica’s Dollars for Docs**

**Categories of Information Disclosed**

- Speaking fees
- Consulting fees
- Research
- Travel fees
- Meals
- Educational items/gifts

Ornstein C, et al. Propublica, 9/7/11

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**Pharmaceutical Companies Influencing Clinical Practice Guidelines – Background (1)**

- For many medical conditions, physicians base their decisions and recommendations regarding diagnostic testing and treatment on standard rules called clinical practice guidelines.

- These guidelines, which are taught in medical schools, residency training programs and continuing medical education courses, routinely play a significant role in doctors’ decisions regarding what medical tests should be ordered, when and what drugs should be prescribed, and when surgery should be performed.

**Pharmaceutical Companies Influencing Clinical Practice Guidelines – Background (2)**

- Because these guidelines typically are adopted widely across the medical profession, they can have a huge impact on medical care, as well as on the sale and use of prescription drugs and medical devices.

- Clinical practice guidelines usually are developed by panels of medical experts convened by medical specialty and disease advocacy organizations.

- Many panel members and most such organizations receive money from the pharmaceutical industry.
Generating Drug Company Profits

\[ \text{# of doctors prescribing a drug} \times \text{# of patients treated with a drug} = \text{X} \]

Conflicts of Interest in Cardiovascular Clinical Practice Guidelines (1)

- Recent study looked at 17 panels that wrote the most recently issued clinical practice guidelines from the American College of Cardiology and the American Heart Association.
- A total of 277 of 498 experts (56 percent) who served on these panels had reported one or more financial conflicts of interest involving drug and device companies. Moreover, 81 percent of the individuals who served as panel chairs or co-chairs or as first authors for the guidelines reported one or more conflicts of interest.


Conflicts of Interest in Cardiovascular Clinical Practice Guidelines (2)

- The types of conflicts of interest for these panel experts included serving as a paid consultant or member of an advisory board to a drug or device company, receiving a research grant or speaking honoraria from a company, or holding stock or other ownership in a company.
- Mendelson’s study identified a total of 221 of 498 experts (44 percent) who reported having no conflict of interest, thus demonstrating that it should be possible to create panels composed only of experts who do not have conflicts of interest.


Conflicts of Interest in Cardiovascular Clinical Practice Guidelines (3)

- Invited commentary on Mendelson study:
  …Mendelson et al raise disturbing questions about the independence and reliability of [clinical practice guidelines] in cardiovascular medicine. The depth and breadth of industry relationships reported in this article is extraordinary. Unexpectedly, financial ties between companies and [the clinical practice guideline] authors include relationships extending far beyond scientific collaboration … To allow such individuals to write [clinical practice guidelines] defies logic. … If we fail as a profession to police our [clinical practice guideline] process, the credibility of evidence-based medicine will suffer irreparable harm.

Nissen S. Arch Int Med. 3/8/11

Pharmaceutical Companies Influencing Clinical Practice Guidelines – Changing Diagnostic Thresholds Can Increase Patient Group

Take Home Messages

• Drug company influence over physician prescribing practices is pervasive.
• Such influence plays a major role in the misprescribing and overprescribing of drugs

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