Advertising Antibiotics
Promoting Resistance

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Points to Cover

- Volume of promotion in Canada
- Influence of promotion on prescribing
  - Sales representatives, sampling, clinical practice guidelines, continuing medical education
- Industry funding and research outcomes
- Advertising of antibiotics in Canada
- Antibiotic prescribing by Canadian doctors
- Conclusions
PROMOTION
Spending on R&D and Promotion, 2002

Promotion
- ~16% of sales*
- $1.9 billion

R&D
- 9.9% of sales
- $1.18 billion

*Estimate based on Eastman Commission Report

PMPRB Annual Report 2002
Spending on Promotion - U.S.

Total spending in the U.S. is $21 billion. The categories include:

- Journal ads: $0.420 billion
- Hospital detailing: $0.861 billion
- Office detailing: $5.300 billion
- DTCA: $11.780 billion
- Samples: $2.630 billion

Spending in U.S. billions of dollars
Total = $21 billion
## Canadian Antibiotic Promotion, 2000

<table>
<thead>
<tr>
<th>Product</th>
<th>Promotional expenditures ($000)</th>
<th>No. of ad pages</th>
<th>No. of details (000)</th>
<th>No. of samples (000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zithromax</td>
<td>2,520</td>
<td>250</td>
<td>44</td>
<td>243</td>
</tr>
<tr>
<td>Biaxin</td>
<td>2,442</td>
<td>160</td>
<td>39</td>
<td>438</td>
</tr>
<tr>
<td>Levaquin</td>
<td>2,225</td>
<td>43</td>
<td>39</td>
<td>153</td>
</tr>
<tr>
<td>Cipro</td>
<td>1,554</td>
<td>188</td>
<td>25</td>
<td>96</td>
</tr>
</tbody>
</table>

IMS Canada, 2001
Credibility of Various Sources of Information

Perceived credibility (0 = not at all, 100 = very)

- CME: 84
- Peer-reviewed journals: 80
- Association meetings: 79
- Single source journals: 64
- Product monographs: 62
- Non-reviewed journals: 53
- DETAILERS: 54
- Detail aids: 51
- Journal ads: 49

Angus Reid, 1991
Percent of Canadian Doctors Using Source of Information

- Detail aids: 41%
- Non-reviewed journals: 44%
- Company sponsored symposia: 45%
- Association meetings: 51%
- Product monographs: 51%
- Journal ads: 53%
- CME: 59%
- Detailers: 66%
- Peer-reviewed journals: 82%

Angus Reid, 1991
# Quality of Information from Sales Representatives

<table>
<thead>
<tr>
<th>Information</th>
<th>Finland 1975</th>
<th>Finland 1986</th>
<th>Australia 1992-94</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indications</td>
<td>91</td>
<td>90</td>
<td>73</td>
</tr>
<tr>
<td>Generic name</td>
<td>78</td>
<td>62</td>
<td>45</td>
</tr>
<tr>
<td>Price</td>
<td>35</td>
<td>29</td>
<td>12</td>
</tr>
<tr>
<td>Side effects</td>
<td>29</td>
<td>27</td>
<td>27</td>
</tr>
<tr>
<td>Contraindications</td>
<td>27</td>
<td>25</td>
<td>0</td>
</tr>
</tbody>
</table>
### Quality of Information from Sales Representatives, France

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Do indications match those on data sheet</td>
<td>65</td>
<td>71</td>
<td>81</td>
<td>80</td>
</tr>
<tr>
<td>Does dose regimen match that on data sheet</td>
<td>74</td>
<td>86</td>
<td>90</td>
<td>92</td>
</tr>
<tr>
<td>Side effects mentioned spontaneously</td>
<td>23</td>
<td>26</td>
<td>29</td>
<td>26</td>
</tr>
<tr>
<td>Contraindications mentioned spontaneously</td>
<td>19</td>
<td>20</td>
<td>24</td>
<td>24</td>
</tr>
<tr>
<td>Drug interactions mentioned spontaneously</td>
<td>17</td>
<td>18</td>
<td>24</td>
<td>23</td>
</tr>
<tr>
<td>Given nature of drug should detailer have mentioned above information</td>
<td>65</td>
<td>81</td>
<td>69</td>
<td>77</td>
</tr>
<tr>
<td>Detailer willing to answer questions</td>
<td>80</td>
<td>69</td>
<td>72</td>
<td>67</td>
</tr>
<tr>
<td>Was detailer convincing</td>
<td>18</td>
<td>17</td>
<td>35</td>
<td>33</td>
</tr>
<tr>
<td>Strong inducements to prescribe drug</td>
<td>24</td>
<td>16</td>
<td>25</td>
<td>39</td>
</tr>
</tbody>
</table>

Prescrire International 1999;8:86-9
## Quality of Prescribing and Use of Sales Representatives

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Question</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Berings, 1994</td>
<td>Relationship between no. detailers seen and benzodiazepine prescribing</td>
<td>No. detailers seen associated with increased prescribing of benzodiazepines</td>
</tr>
<tr>
<td>Bower, 1987</td>
<td>Reliance on detailers as source of information about new drugs &amp; frequency of generic prescribing</td>
<td>Those who rely “a great deal” tend to prescribe fewer generics</td>
</tr>
<tr>
<td>Caudill, 1996</td>
<td>Relationship between credibility of information from detailers &amp; cost of prescribing</td>
<td>Significant positive relationship between cost of prescribing and positive attitudes toward pharmaceutical representatives</td>
</tr>
<tr>
<td>Powers, 1998</td>
<td>Relationship between interaction between GPs and detailers and prescribing for hypertension</td>
<td>Those with greatest amount of interaction significantly more likely to prescribe ACE inhibitors and/or calcium antagonists versus thiazides</td>
</tr>
</tbody>
</table>
Do Doctors Know if They’re Being Influenced?

Rating of Factors Influencing Choice of Drug

Do Doctors Know if They’re Being Influenced?

- “Impaired cerebral blood flow is a major cause of senile dementia
  - 71%
- “Cerebral vasodilators useful in managing confused geriatric patients
  - 32%
- Darvon (dextropropoxyphene):
  - stronger than ASA--49%
  - equivalent to ASA--31%
  - weaker than ASA--20%

Differences Between Study Time Periods

<table>
<thead>
<tr>
<th>Samples available (Period 1)</th>
<th># (% of Patients Prescribed First-line Medications by Residents)</th>
<th># (% of Patients Prescribed First-line Medications by Faculty)</th>
<th># (% of Patients Prescribed First-line Medications by all Physicians)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>15 (39%)</td>
<td>6 (35%)</td>
<td>21 (38%)</td>
</tr>
<tr>
<td>Samples unavailable (Period 2)</td>
<td>34 (72%)</td>
<td>18 (47%)</td>
<td>52 (61%)</td>
</tr>
</tbody>
</table>

Boltri et al. Family Medicine 2002;34:729-31
Clinical Practice Guidelines
## Relationships Between Guideline Authors and Pharmaceutical Industry

<table>
<thead>
<tr>
<th>Relationship</th>
<th>No. of authors (%) [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Had relationship with companies whose drugs were considered in the guidelines process</td>
<td>47/80 (59) [48-70]</td>
</tr>
<tr>
<td>Relationship predated guideline process</td>
<td>45/47 (96) [92-100]</td>
</tr>
<tr>
<td>Relationship postdated guideline process</td>
<td>25/47 (53) [39-67]</td>
</tr>
<tr>
<td>Believed that relationships influenced personal recommendations</td>
<td>5/68 (7) [1-9]</td>
</tr>
<tr>
<td>Believed that relationships influenced recommendations of colleagues</td>
<td>13/67 (19) [8-30]</td>
</tr>
</tbody>
</table>

Declarations of Conflict-of-Interest in Guidelines

<table>
<thead>
<tr>
<th>Type of declaration</th>
<th>No. of guidelines making declarations regarding authors’ financial interactions (n=44)</th>
<th>No. of guidelines making declarations regarding guideline creation process (n=44)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No declaration made</td>
<td>42</td>
<td>26</td>
</tr>
<tr>
<td>Declared that no sponsorship received</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Received nonpharmaceutical industry support</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td>Received pharmaceutical industry support</td>
<td>1</td>
<td>11</td>
</tr>
</tbody>
</table>

Continuing Medical Education
CME Events in USA - 2000

- 314,022 industry sponsored meetings & events for doctors
- $1.9 billion
- 78,500 (25%) CME events

Scott-Levin, March 2001
Effects of Sponsorship on Content of CME

Presentation of company and noncompany drugs

Company drug
Noncompany drug
Course 1
Course 2

Equivocal: 35%, 14%, 16%, 34%
Negative: 32%, 33%, 21%, 20%
Positive: 51%, 35%, 64%, 47%

Bowman. Mobius 1986;6:66-9
Effects of CME on Prescribing Patterns

Percent prescribing drug most frequently to new patients

Course 1
Before: Verapamil 12.3%, Nifedipine 38.4%, Diltiazem 13.7%
After: Verapamil 9.3%, Nifedipine 51.9%, Diltiazem 16.7%

Course 2
Before: Verapamil 9.9%, Nifedipine 30.6%, Diltiazem 22.3%
After: Verapamil 5.8%, Nifedipine 20.7%, Diltiazem 33.9%

Effects of “CME” on Volume of Prescribing

Before a Free Trip — And After

Researchers tracked the change in prescriptions written for a new intravenous antibiotic at one hospital after a pharmaceutical company invited physicians on an all-expenses-paid trip to a luxurious West Coast resort where the drug was promoted.

- Drug is added to hospital formulary.
- Invitations arrive for the trip.
- Doctors meet at the resort.
- Prescriptions for the drug spike after promotion.

Prescribing at major medical institutions
Outcome of Company Funded Research
Recommendations and Funding

Higher the score, the more strongly the treatment is recommended

Kjaergard et al. BMJ 2002;325:249
Publication Bias in Industry Funded Research

Publication of trials submitted to Swedish regulatory authorities

- Studies showing significant differences between efficacy of drug and placebo 3 x more likely to appear as stand alone publications
- Intention to treat and per protocol analyses used in submissions to regulatory authorities but only 24% of stand alone journal publications used intention to treat analysis
- High frequency of duplicate publication due to inclusion of different subsets of studies in several pooled publications

Melander et al. BMJ 2003;326:1171-3
Outcome of Industry Funded Research

Odds ratio meta-analysis plot (fixed effects)

Azimi et al (15)
Cho et al (17)
Clifford et al (18)
Davidson (19)
Dieppe et al (21)
Djulbegovic et al (22)
Djulbegovic et al (23)
Friedberg et al (26)*
Friedberg et al (26)**
Kamal-Bahl et al (29)#
Kamal-Bahl et al (29)##
Koep et al (33)
Mandelkern (35)
Sacristan et al (39)^
Sacristan et al (39)^^
Thomas et al (41)
Vandenbroucke et al (42)
Yaphe et al (44)

MH pooled odds ratio = 4.051419 (95% CI = 2.978525 to 5.510779)

Lexchin et al. BMJ 2003;326:1167-70
Proof of Effectiveness: "Pharma-Ads"

Benchmark Study 1993

COMPLIMENTS OF WILLIAMS & WILKINS

THE AD PROMOTES

THE AD WORKS!

Arbeitsgemeinschaft
LA-MED

Leseranalyse medizinischer Zeitschriften e. V.
Sir Alexander Fleming discovered penicillin 75 years ago.
He also predicted that antibiotic resistance might one day threaten his discovery.

The good news is that Canada is a world leader in the fight against antibiotic resistance.
Our greatest threat now is complacency. If we don’t use antibiotics responsibly,
they won’t work when we really need them.

So please remind patients that:

- antibiotics are not effective against colds and flu
- if prescribed antibiotics, they should take them as directed
- they must always finish their antibiotics, even if they start feeling better
- antibiotics are prescribed for them alone and must never be shared

For more information, please visit www.antibiotics-info.org
“Back on track from otitis media in just three days”
Azithromycin Prescriptions, Ontario 1999

- Acute bronchitis: 38%
- Otitis media: 15%
- Pneumonia: 27%
- Acute sinusitis: 7%
- Acute URTI: 4%
- Others: 9%

Legend:
- Acute bronchitis
- Otitis media
- Pneumonia
- Acute sinusitis
- Acute URTI
- Others
“For the treatment of respiratory tract infections”

“Abbott Laboratories . . . [is] committed to the appropriate use of antibiotics”

For the treatment of respiratory tract infections

comes from strength

BIAXIN
ELAMITHROMYCIN
We invented tough.

Abbott Laboratories, Limited recommends Biaxin as a second-line agent. We are committed to the appropriate use of antibiotics and support anti-infective clinical practice guidelines.

The majority of adverse reactions in clinical trials were mild to moderate. The most frequent were nausea (1%) and diarrhea (2%).

Biavin is indicated for mild-to-moderate infections: acute bacterial exacerbation of chronic bronchitis caused by S. pneumoniae, M. catarrhalis (including beta-lactamase-producing strains) and P. aeruginosa (including beta-lactamase-producing strains), and pneumonia caused by S. pneumoniae and M. pneumoniae.

Biavin is contraindicated as concurrent therapy with steroids, tetracyclines, disulfiram or ethanol.

Biavin should not be used in pregnancy except where no alternative therapy is appropriate, particularly during the first 3 months of pregnancy.

If pregnancy occurs while taking the drug, the patient should be advised of the potential hazard to the fetus.

Consult prescribing information for important safety information and drug interactions.
IN ACUTE Otitis MEDIA

An earful of comfort for your little patients.

Little comforts add up to big comfort with Pediatric Biaxin. It offers proven clinical success in acute otitis media and LRTIs. With effective coverage against typical, atypical and beta-lactamase-producing respiratory pathogens. The convenience of b.i.d. dosing. And the good taste of wild berry flavour. That’s why you and your patients can take comfort in Pediatric Biaxin.

Abbott Laboratories, Limited recommends Pediatric Biaxin as a second-line agent. We are committed to the appropriate use of antibiotics and support anti-infective clinical practice guidelines.

Pediatric
CLAIRMHYCIN SUSPENSION

Big comfort for little patients.
CONTRAINDICATIONS: AMINDICATIONS AND USAGE: BIAxin CLARITHROMYCIN SUSPENSION 40 mg, and 200 mg daily for at least 3 weeks before the initiation of clarithromycin. The clarithromycin CLARITHROMYCIN SUSPENSION 40 mg, and 200 mg daily for at least 3 weeks before the initiation of clarithromycin. The clarithromycin CLARITHROMYCIN SUSPENSION 40 mg, and 200 mg daily for at least 3 weeks before the initiation of clarithromycin.


d of the indication must be considered in the course of therapy. clarithromycin has been shown to reduce the incidence of gastrointestinal side effects, it has been shown to be effective in the treatment of the symptoms of gastric and duodenal ulcers. clarithromycin has been shown to be effective in the treatment of the symptoms of gastric and duodenal ulcers. clarithromycin has been shown to be effective in the treatment of the symptoms of gastric and duodenal ulcers.


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Clarithromycin Prescriptions, Ontario 1999

- Acute bronchitis: 32%
- Acute sinusitis: 13%
- Pneumonia: 10%
- Otitis media: 6%
- Other: 13%
Who’s at risk?

“Bayer supports the appropriate use of antibiotics”

“Risk factors include severe infections, frequent infections, COPD and comorbid conditions”
“An appropriate first choice for your RTI patients at risk”
Ciprofloxacin Prescriptions, Ontario 1999

- Urinary tract infection: 21%
- Acute bronchitis: 15%
- Pneumonia: 8%
- Acute sinusitis: 5%
- Other: 51%
Prescribing for Otitis Media

British Columbia, family physicians
“9-month old previously healthy, fever 38.5°C, pulling at right ear, tympanic membrane slightly pink, retracted and decreased mobility”

Canadian Family Physician 2001;47:521-7
Prescribing for Acute Sinusitis

British Columbia, family physicians “after how many days illness would you begin antibiotics for 4-yr old with daytime cough and bilateral purulent nasal discharge”

Canadian Family Physician 2001;47:521-7
Prescribing for Saskatchewan Preschool Children, 1995

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>No. of children</th>
<th>Percent receiving antibiotics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute URI</td>
<td>23,255</td>
<td>49</td>
</tr>
<tr>
<td>Acute bronchitis or bronchiolitis</td>
<td>5,473</td>
<td>65</td>
</tr>
<tr>
<td>Common cold</td>
<td>4,743</td>
<td>18</td>
</tr>
<tr>
<td>Serous otitis media</td>
<td>2,515</td>
<td>32</td>
</tr>
<tr>
<td>Acute laryngitis, croup</td>
<td>2,647</td>
<td>44</td>
</tr>
<tr>
<td>Influenza</td>
<td>1,971</td>
<td>24</td>
</tr>
</tbody>
</table>

Clinical Infectious Diseases 1999;29:155-60
Inappropriate Prescribing of Antibiotics

- Use of antibiotics in conditions where they are usually not warranted
  - Acute sinusitis, acute otitis media, acute bronchitis, common cold
- Use of non-first line antibiotics
  - Treatment of pneumonia, urinary tract infection
- What effects will this have on resistance?
Conclusions

- Promotion works
  - Doctors are influenced sometimes without being aware of it
- The information behind promotion is biased
- Canadian journal ads for antibiotics promote inappropriate prescribing
- Antibiotic prescribing by Canadian doctors is often inappropriate
- What effect will this type of prescribing have on antibiotic resistance?