Industry & Us

Research Funding: What is Funding Worth?

- Funding gives an OR of 4-5.3 that,
  - Study outcomes favor therapy studied
  - Therapy is recommended as Treatment of Choice

1. JAMA, 2003; 290: 921-8. BMJ, 2003; 326: 1167-70. CMAJ 2004;170(4): 477-83.

How Does Funding Result in Bias?

- Pick your Battles: Poor Comparators
- Trial Design: e.g. Run-in
- Selective Publication (Publication Bias)
- Selective Reporting (Publication Bias in situ)
  - Secondary Endpoints,
  - Surrogate Markers
  - Subgroups
- Stats:
  - Relative risk over Absolute (real) risk
  - Statistical over Clinical Significance

1. JAMA, 2003; 290: 921-8. BMJ, 2003; 326: 1167-70. CMAJ 2004;170(4): 477-83.

Picking your Battles: Unequal Comparators

- Atenolol is an inferior hypertensive agent yet it is the "reference" in >5 major trials[1]
- COMET compared Metoprolol vs Carvedilol. Metoprolol dose was 2/3 of Carvedilol.[2]
- Oral Amphotericin vs Fluconazole (has poor oral absorption).[3]

1. Lancet 2004; 364: 1684-9. 2. Lancet. 2003;362:7-13. 3 Ann Intern Med. 1994;120:913-8

Trial Design: Example Run-in

- Run-in = A pre-trial period in which patients take placebo or drug and are monitored for
  - Compliance
  - Benefit
- This "runs-around" ITT and is believed to falsely enhance Treatment effect[1]
- Some examples:
  - Tegaserod trial use Run-in to find compliers[2]
  - Statin (High vs Low) use Run-in to pick only those having significant LDL reduction. [3]

1. JAMA. 1998;279(3):222-5. 2. Am J Gastroenterol 2005; 100:362-372 3. NEJM 2005; 352: 1425-35.

Publication Bias

- Once a Trial starts, there are 4 options
  1) Not Finished, Not Published
  2) Not Finished, Published
  3) Finished, Not Published
  4) Finished, Published.
- Option 4 is what we commonly see.
- What about Option 3?

Publication Bias: Trial Done, Not Published

- Of Trials completed, 62-67% not published.[1]
- Even if printed as abstracts in mid-level journal, 39% never published in full (even after 20 years)[2]

1. BMJ 2005;331:19. Emerg Med (Fremantle).2001;13:460-4. Radiology. 2004;232:101-6. 2. Intern Med J. 2003 Apr;33(4):192-4.

Publication Bias: Who is responsible?

- Are journals responsible
  - Likely not [1] (only 5%)
- Are Authors (and Industry) responsible
  - Authors: Yes
    - (Authors choice to not publish or publish in "grey literature" 10X > Journal Rejection)[2]
  - Industry: Yes[3]

1. Med J Aust 2006; 184:621-6. JAMA 2002;287:2825-8. *BMJ* 2005;331;19. 2. *BMJ* 2005;331;19. 3 BMJ 2003, 326: 1167-70. *BMJ* 2005;331;19.

Research 2

Selective Publication

Rare cross referencing

Changing authors & Definitions

Publications from Single Trails:

- if trial +ve = 90%

- if trial –ve = 29%

Melander et al. BMJ, 2003; 326: 1171-73

Research 3

- **Withhold Potentially Hazardous information.**
  - **Paroxetine found to be no better and perhaps worse than placebo in under age 18.**
  - **World-wide Sales = $4.97 bill in 2003**
  - **GSK Internal Document *"It would be commercially unacceptable to include a statement that efficacy had not been demonstrated"***
- **Pfizer: Hid ½ the data on Celebrex (CLASS)**
- **Immune Response Co: Sued doctors who published a negative trial.**

Kondro & Sibbald. CMAJ. 2004; 170(5): 783 Angell, Truth about Drug Co. 2004

Research 4

- **Buy influence beyond the study:**
- Pay Doctors to Recruit
  - E.g.: $12K/pt + $30K after 6= 100+K
- These doctors write supportive editorials and letters for your product (87% vs 20% those who've never seen your money).

Stelfox et al, NEJM 1998, 338: 101-6.

Publication Bias *in situ*: Incomplete Reporting

- In general literature: Reporting poor
  - for all outcomes (31-50%)
  - for harm (59-65%)[1,2]
- "Incomplete reporting" more common in Industry (61%) vs non-industry (39%) funded,
  - Peds SSRI: 6 trials used 42 measures but only 14 showed any improve and didn't report the rest.[3]
- Linked to Multiple Analysis/ Bias but degree unknown[4]
  - (good papers (e.g. ALLHAT)[5] correct for it)

1. CMAJ 2004; 171:735-40. 2. JAMA 2004;291:2457-2465. 3. Lancet 2004;363:1341-5. BMJ 2004;328:879-83. 4. J Med Internet Res. 2004;6:e35. 5. JAMA 2002; 288:2981-97

Secondary Endpoints: the Vitamin A story

- Example Vitamin A vs Placebo
- Beneficial effects = significant reduction in non-fatal MI (14 vs 41)
- But non-significant increase in Vitamin A group for
  - cardiovascular deaths (27 vs 23)
  - All-cause mortality (36 vs 27)
- "We conclude that,… Vitamin A treatment substantially reduces non-fatal MI."
- All cause mortality was later shown to increase (NNH 326)[2]

1. Lancet 1996; 347: 781-86 2. Lancet 2003;361:2017-23.

Surrogate Markers:

- Encainide/flecainide[1]: ↓ extra beats after MI
  - But Killed 1 in every 21 people
- Vitamin A and E[2] are anti-oxidants
  - But killed 1 in every 326 and 257 (respectively)
- Fibrates[3] reduce Triglycerides and LDL
  - But kill 1 in every 134 people (in 4.4 years)

1. NEJM 1989; 321(6): 406-12. 2. Can Fam Phys 2005; 51:1471-2. 3. Arch Intern Med. 2005;165 :725-30

Sub-Group Analysis

- Sub-group analysis generate spurious and inflated results.
- Concerns
  - The trial was powered for them
  - Positive results = data mining unless *a priori*
- They should be looked at only in regards to "hypothesis generation"
- No relevance to the EBM Consumer.

Am Heart J. 2006;151:257-64. Stat Med. 2000 Dec 30;19(24):3325-36. J Clin Epidemiol. 2004 Mar;57(3):229-36. Health Technol Assess. 2001;5(33):1-56

Part 3: Some Arguments

Industry side

- "Our Innovation and development yield life saving therapies (and relieve of suffering)"
- 5,000 to 14,000 molecules to get one drug
- $802 million/ marketable drug
- Up to 15 years to get a drug to market.

- Responsibility to Share-holders

DiMasi J Health Econ. 2003 Mar;22(2):151-85. * *Anon*, Prescrire Int. 2004;13(69):32-6.

Innovation

- Me-too drugs:
  - E.g Ace inhibitors: one new drug, 10 me-too agents.
- Patent Extenders:
  - Lipidil Supra, Esomeprazole, Paxil CR, etc.
  - Why: Lexapro = fastest growing SSRI (8 million patients)

www.celexa.com, Angell Truth About Drug Companies, 2004 (pg 65)

True Innovation

- How much true innovation:
  - Unique drugs = 14% new applications
  - Between 98-02, average of 12/year
- Who does the research:
  - Of the 21 most beneficial drugs: 15 (71%) started public
  - Of the top 5 drugs (of 1995), 94% of the original research is publicly funded.

Angell Truth About Drug Companies, 2004 (pg 54 & 65)

Cost

- $802 million Not average cost:
  - Only truly innovative
  - And most innovative from publicly funds
- Subtract
  - 399 mill (≈50%): Theoretic lost revenue (if alternate investment)
  - 137 mill in Tax credit and incentives (up to 50%
- Others put the amount around 100 million

Promotion Spending

- **In 98, $12.7 Billion on US Drug Promotion**
  - **6.6 Billion on drug samples**
  - **3.5 Billion on office promotion**
  - **0.7 Billion on hospital promotion**
  - **½ Billion on Medical Journals**
  - ***1.3 Billion on DTC (* Fasting growing)***
- **>50% on the top 50 drugs**
- **(In Canada = 1.7 billion/yr on Drug promotion)**

Ma et al. Clin Ther 2003; 25(5): 1503-17. Wolfe SM. J Gen Intern Med 1996 .

How do we See Ourselves:

- **"I am not influenced"**
- **The more we accept, the more likely (and more strongly) we believe statement #1.**
- **We would not wear industry logo (87%),…**
- **but 97% carry industry products with logos**
- **"Others are probably more influenced"**
- **Even when we think we are influenced, we still take the goodies**

Hodges B. CMAJ 1995 Sep 1;153(5):553-9 & Wazana JAMA 2000 Jan 19;283(3) : 373-80 Sigworth et al JAMA 2001:286: 1019-25. Choudhry et al. JAMA 2002; 287: 612-17. Sergeant et al. CMAJ 1996; 155(9):1243-48.

More Lies we tell Ourselves

- **"I prescribe on best evidence" - NO**
- **"I consider costs to the pt" - NO (76.6% can not get within 25% of drug costs)**
- **"I can't even remember the name of the, …" – Doesn't matter, seed is planted**
- **"Aside from influence, it's a good source of CME" – Information wrong 11-42%**
- **"I know the difference between good & bad information." – No, We can't tell**

Soumerai et al. Milbank Q. 1989; 67:268-317. Anderson et al. CMAJ. 1996; 154(7): 1013-17. Allan GM et al. Can Fam Phys2004; 50: 263-70. Wazana JAMA 2000 Jan 19;283(3):373-80. Ziegler et al. JAMA 1995; 273: 1296-8. Stryer et al. J Gen Intern Med 1996; 11:575-83

How do we See Industry:

(Dichotomy of Greed and Ethics)

- **We want everything we can get.**
  - **39% wanted money for CME**
  - **Want gifts (or no contact)**
  - **We recognize that industry often poor source (but still go)**
- **It is no wonder that some in Industry are tired of us**
  - **insulting them with our hand-out**

Med Post 2003, Oct 28. Hodges B. CMAJ 1995 Sep 1;153(5):553-9. A sad response from a drug rep. Anonymous. bmj.com, 22 Dec 2000

Part 4: Some Guidelines?

The Guides

- Training in University
  - 25% of Can FP have policies
  - 58% US FP have policies (41% prohibit).
  - 35% US Int Med policies (<12% prohibit).
  - After 1 school banned industry, interactions were 82% level before ban.
- CMA Guidelines:
  - Last update 2001.
- Industry Policies:
  - Canada's Research-Based Pharmaceutical Companies. Code of marketing practices (last update 2003)

Mahood et al. Can Fam Phys 1997; 43: 1947-51. Brotzman et al. J Fam Pract 1992; 34(1): 54-7. Lichstein et al. Arch Intern Med 1992; 152: 1009-13.Brody. Health Affairs 2002; 21(2): 232-234

CMA Guidelines

- In research – Pt 1st, ethics, consent, pub results, enroll money (not entice) with pt aware & inform j of all relationships.
- CME – Education 1st, no product names, no peer selling*, posters not in same room & No money for travel, time, accommodation, etc (learners may if unconditional to acad instit).
- Samples (MD responsible for exp dates)
- No money for promotional meetings & No gifts (ever)
- Teaching aids etc okay (with Co Name but never drug name)

Enforcement

- **We (physicians) have none!**
- **Industry is doing better than us**
- **RX&D (Canada's Research-Based Pharmaceutical Companies) have fines for violation of their policies: $1-15,000 (but Pfizer made 32 Billion in 2001).**

Sibbald. CMAJ 2002; 167 (5): 522.

Do these sound grievous?

- **Bayer Inc. $15 000: only 50 minutes of education for over 4 hours of entertainment, (round of golf, tour of a brewery and dinner)**
- **Merck Frosst $1000: CME event 30 minutes less than the free dinner.**
- **SmithKline Beecham $1000: Discussion of trial then Ballet's presentation of *The Nutcracker*. (Spouses welcome) it paid for a social activity other than meals.**
- **SmithKline Beecham $5000: 1-hour lecture then "salsa lesson" then dinner."**

Sullivan CMAJ: 2000; 163 (6)

What we can do?

- Choose non-biased CME
- Do Alternative CME: Like PBSGL or a "journal club" : Claim some, write off the rest.
- If you meet reps, don't fight but get the paper & actually look at (don't prescribe until you do)
- If you go to industry funded events, look for influence & recognize you are being influenced
- READ