“There is a foolish corner in the brain of the wisest man.”

Aristotle, philosopher (384-322 BC)
Commercial Bias in Psychiatry
Literature & Practice
And What You Can Do About It

Objectives
• To describe specifics of commercial bias in psychopharm
  – Manifestations
    • Literature
    • Clinical practice
  – Internal documents
• To apply specific strategies to mitigate commercial influence

Disclosure
No financial conflicts of interest.

Gotzsche et al, 2007
• Industry-initiated trials submitted to REB
• 40 of 44 trials had unacknowledged authors
• 64% of studies list co employees as authors
• No protocol listed clinical investigators as being part of analysis or writing

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Pfizer, Current Medical Directions
• 85 manuscripts on sertraline
• Uniformly positive
• Side effects under-reported
• 18 to 40% of articles on sertraline in Medline from 1998-2000
• Higher impact factor journals

Sismondo, 2007

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"gaining product adoption and usage through the systematic, planned dissemination of key messages and data to appropriate target audiences at the optimum time using the most effective communication channels… publications, journal reviews, symposia, workshops, advisory boards, abstracts, educational materials/PR."

Sismondo, 2007

**CASPPER**

- AJP, JAACAP (Edwards, 2009)
- "Designed to make this process as simple as possible for interested physicians"
- "Develop a topic… strengthen the product positioning"
- "benefit the sales force by expanding the database of published articles"
- "work closely c contributing physicians to ensure rapid dissemination of consistent data and messages"

**Quetiapine…**

The following table is an attempt to simplify the claims that could be obtained from these results. A is entered for those comparisons where we have a statistically significant benefit, but with "all others" or with high dose Seroquel, and be it using observed cases or using LOGIC. A marks those comparisons where a comparator has demonstrated significant superiority compared to Seroquel.

<table>
<thead>
<tr>
<th>Comparator</th>
<th>Category</th>
<th>Acute</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoxetine</td>
<td></td>
<td>/</td>
<td></td>
</tr>
<tr>
<td>Rapipenthone</td>
<td></td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Clozapine</td>
<td></td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Risperidone</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Other opioids</td>
<td></td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>

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Quetiapine Study 15

- Pts c SCZ randomized to haloperidol or quetiapine for 1 year
- Pts on haloperidol lower Sx ratings, and fewer relapses
- Data ‘cherry picked’, & trial published (Velligan et al, 2002) as “positive impact on important domains of cognitive performance that have been found to predict role function and community outcomes”

Spielmans & Parry, 2010

Selective Publication...

- Turner et al, 2008
- Studies submitted to FDA
- 12 antidepressants

Data from Turner et al, 2008
COI & study outcome

<table>
<thead>
<tr>
<th>Variable</th>
<th>N (SIS)</th>
<th>N (All)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All clinical trials</td>
<td>101</td>
<td>180</td>
</tr>
<tr>
<td>Author COI = 4.9 times positive results</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Industry-supported study = 8.4 times positive results</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All clinical trials in AJP, AGP, J Clin Psych, J Clin Psychopharm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2001-2003</td>
<td></td>
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</tbody>
</table>

Perlis et al., 2005

Our Literature

- "Author TBD" (Matheson, 2016; Braun, 2013; Wislar et al., 2011; Sismondo, 2007; Gotzsche et al., 2007)
- Reporting bias (Boshi, 2016; Scott et al., 2015; Hughes et al., 2014; Saini et al., 2014; Dank et al., 2014; Micaulay et al., 2010; Mathieu et al., 2009; Vedula et al., 2009; Rising et al., 2008; Chan & Altman, 2005; Chan et al., 2004; Melander et al., 2003)
- Selective publication (Jones et al., 2013; Wager et al., 2013; BMJ 2012; Shamiyian & Kane, 2012; Carrasco et al., 2012; Turner et al., 2008)
- COI & study outcome (Ahn et al., 2017; Flaco et al., 2015; Xu et al., 2013; Lundh et al., 2012; Heres et al., 2006; Perlis et al., 2005; Fries & Krishnan, 2004; Lexchin et al., 2003)
- CPGs (Cosgrove et al., 2017, 2013; Jefferson et al., 2017; Lin et al., 2017; Shnier et al., 2016; Kung et al., 2012; Neuman et al., 2011; Choudhry et al., 2002)

Promotion & Rx behavior

- Quality lower
- Quantity higher
- Cost higher
- No evidence of improvement

Spurling et al., 2010; Zipkin & Steinman, 2005; Manchanda & Honka, 2005; Wazana, 2000

“SSRIs for Autism…”

Carrasco et al., 2012

…”Selective Publication…”

“At present, results of most clinical studies of children are unavailable to the pediatric research community and the public.”

Scott Denne, 2012

“…Selective Publication…”

“Now, it is simply no longer possible to believe much of the clinical research that is published, or to rely on the judgment of trusted physicians or authoritative medical guidelines. I take no pleasure in this conclusion, which I reached slowly and reluctantly over my two decades as an editor of The New England Journal of Medicine.”

Marcia Angell, 2009
Expanding Markets…

Olz & bipolar

- “The company is betting the farm on Zyprexa. The ability of Eli Lilly to remain independent and emerge as the fastest growing pharma company of the decade depends solely on our ability to achieve world class commercialization of Zyprexa.”

- 1997 document: Sales projections would increase fourfold if olz could be viewed as a “Depakote-like MOOD-STABILIZER” rather than a “Risperdal-like…Antipsychotic”

- “To be a leader in the bipolar market, Zyprexa will need to be viewed as a true mood stabilizer.”

- According to same document, though, the company did not yet have the data to support this. 

...Expanding Markets…

Olz & bipolar

- “Expand our market by redefining how primary care physicians identify, diagnose and treat complicated mood disorders”

- “complicated mood… untapped growth potential”

- Fictional case vignettes that did not meet DSM criteria for BD I created for sales reps to use

- “Doctor, would you agree that you see patients who present with Sx of mood, thought and behavioral disorders who are not responding to your satisfaction”

...Overdiagnosis of BD…

- Goldberg et al, 2008
  - Retrospective chart review
  - 85 adults with substance abuse, admitted to inpatient unit over 1 year period
  - only 33% met DSM criteria

- Zimmerman et al, 2008
  - 700 psychiatric outpts c Dx of BD
  - <1/2 met criteria using SCID

...Trends in BD Dx…

- Moreno et al, 2007

Antipsychotics for youth in BC

- Ronsley et al, 2013
In Practice

• **BD Dx** (Moreno et al, 2007; Goldberg et al, 2008; Zimmerman et al, 2008; Levin & Parry, 2011; Mitchell, 2012)


• **Polypharmacy** (Rotermann et al, 2014; Mangin, 2014; CIHI 2014; Farrell et al, 2013; Mojtabai & Olfson, 2010; Essock et al, 2009)

• **Nursing homes** (CIHI 2016, 2012; BCMOH 2011; Rochon et al, 2007)

Answers/Solutions??

Suggestions??

"Science is at once the most questioning and the most skeptical of activities and also the most trusting. It is intensely skeptical about the possibility of error, but totally trusting about the possibility of fraud."

Arnold Relman, 1989

Your own critical reviews

• Relevance / importance
• Methods, methods, methods
• clinicaltrials.gov
• Follow the money: funding source, authors
• Abstract / conclusions for bias
• Narrative

***Your judgment!***
Methods

- Participation criteria
- Number of investigators / sites
- Outcome measure (relevance, consistency)
- Comparator choice
- Comparator dosing (high, low, titration, timing)
- Adverse events (collection, reporting, explaining)
- Study length

Professional Independence

- No need to keep on top of everything – most of the literature is…
- Avoid commercial sources
- Follow the money
- Don’t hesitate to question widely-accepted beliefs
- Tolerate uncertainty

Caution

- Supplements
- MECCs
- “free”
- Flashy / easy / simple
- COI (non-)disclosures
- **Follow the money**

Resources

- Prescrire International
- Therapeutics Initiative
- Worst Pills, Best Pills
- RxISK
- Grey Literature (ex. Turner, 2013)

Clinical Practice

Hippocratic Psychopharmacology

- Some, not all, diseases be Tx
- Tx enhance natural healing process, not artificial cures
- Tx diseases, not Sx
- Meds guilty until proven innocent

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Rational Rx

• Beyond drugs
• Strategic
• Vigilance re adverse effects
• Caution & skepticism
• Shared agenda
• Long-term, broader impacts

**Schiff et al, 2011**

Summary

• Commercial bias pervades medical literature, education and practice

• Solution starts with us
  – Healthy skepticism
  – Independence
  – Challenging and rewarding!

“To have the placid faith of the simple believer, instead of the fighting faith of the aggressive doubter, has ever been our besetting sin in the matter of treatment.

In the progress of knowledge each generation has a double labour – to escape from the intellectual thralls of the one from which it has emerged and to forge anew its own fetters.”

William Osler, address to OMA, 1909
COI & study outcome

TABLE 1. Conflict of Interest, Industry Funding, and Outcome of Published Clinical Trials

<table>
<thead>
<tr>
<th>Variable</th>
<th>Studies With Conflict of Interest Present</th>
<th>All Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Industry Funding</td>
<td>Industry Funding</td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>Yes</td>
</tr>
<tr>
<td>All clinical trials</td>
<td>187a</td>
<td>147</td>
</tr>
<tr>
<td>Randomized, double-blind, placebo-controlled trials</td>
<td>75b</td>
<td>67</td>
</tr>
<tr>
<td>Drug &gt; placebo</td>
<td>69c</td>
<td>63c</td>
</tr>
<tr>
<td>Drug ≤ placebo</td>
<td>6</td>
<td>4</td>
</tr>
</tbody>
</table>

a Includes employees (119 of 397, 30.0%), stockholders (25 of 397, 6.3%), and consultants or speakers receiving fees (114 of 397, 28.7%).
b Includes employees (62 of 162, 38.3%), stockholders (12 of 162, 7.4%), and consultants or speakers receiving fees (34 of 162, 21.0%).
c Association between author conflict of interest and positive outcome among all studies and among industry-funded studies (p<0.001, Fisher’s exact test).
d Association between author conflict of interest and positive outcome among non-industry-funded studies (p=1.00, Fisher’s exact test).

• Author COI=4.9 times positive results
• Industry-supported study = 8.4 times positive results
• All clinical trials in AJP, AGP, J Clin Psych, J Clin Psychopharm
• 2001-2003

Perlis et al, 2005