

# Evidence-based Synthesis Program (ESP)



## Using Comparative Effectiveness Review Findings in Practice: A new model

Mark Helfand, Director  
ESP Coordinating Center

October 2013

# Learning Objectives

- Recognize the clinician's role in ensuring that the evidence base is complete.
- Become familiar with rhBMP-2 (bone morphogenetic protein 2) and other landmarks in reporting bias.

# “EBM 1”

As clinicians, we want to base treatment decisions on all of the relevant clinical research data.

“What is the kind and strength of the evidence I am relying on to make a recommendation to a patient?”

# “EBM 1”

- Systematic reviews are a cornerstone of “EBM 1”.

# Systematic literature reviews

- are systematic to remove bias in finding and reviewing the literature.
- Emphasize the best evidence
  - ⑩ Valid
  - ⑩ Reflects patients' concerns
- Synthesize, don't just list

# Systematic literature reviews

- are systematic to remove bias in finding and reviewing the literature.

*Experts may underplay controversy or select only supportive evidence*

**Conclusions:** During 6 weeks' treatment, ziprasidone and olanzapine demonstrated comparable antipsychotic efficacy. Differences favoring ziprasidone were observed in metabolic parameters.

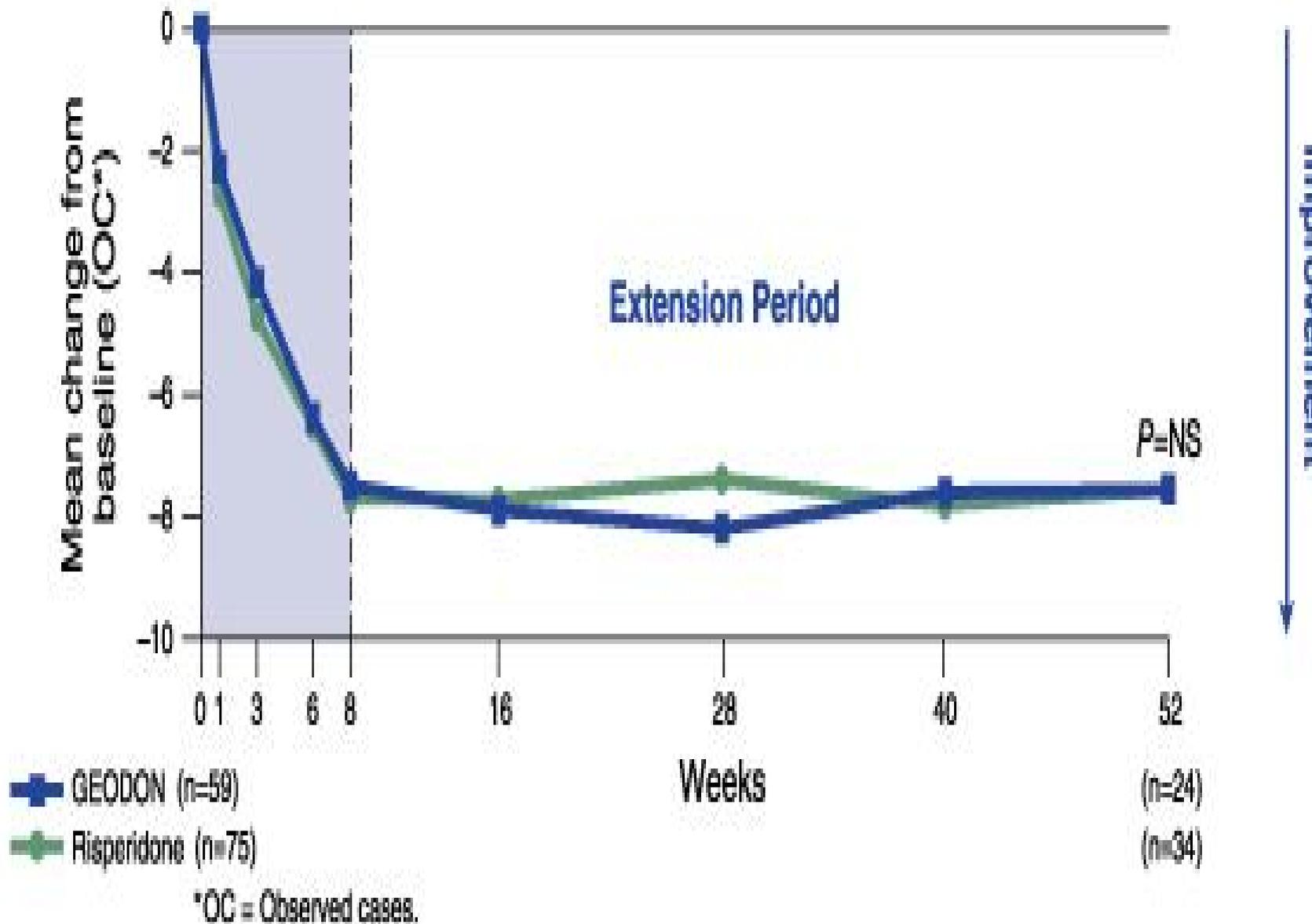
*Simpson et al, 2004*

**TABLE 3. Treatment-Emergent Adverse Events in Patients With Schizophrenia or Schizoaffective Disorder in a 6-Week Randomized, Controlled, Double-Blind Trial of Ziprasidone and Olanzapine, by Body System**

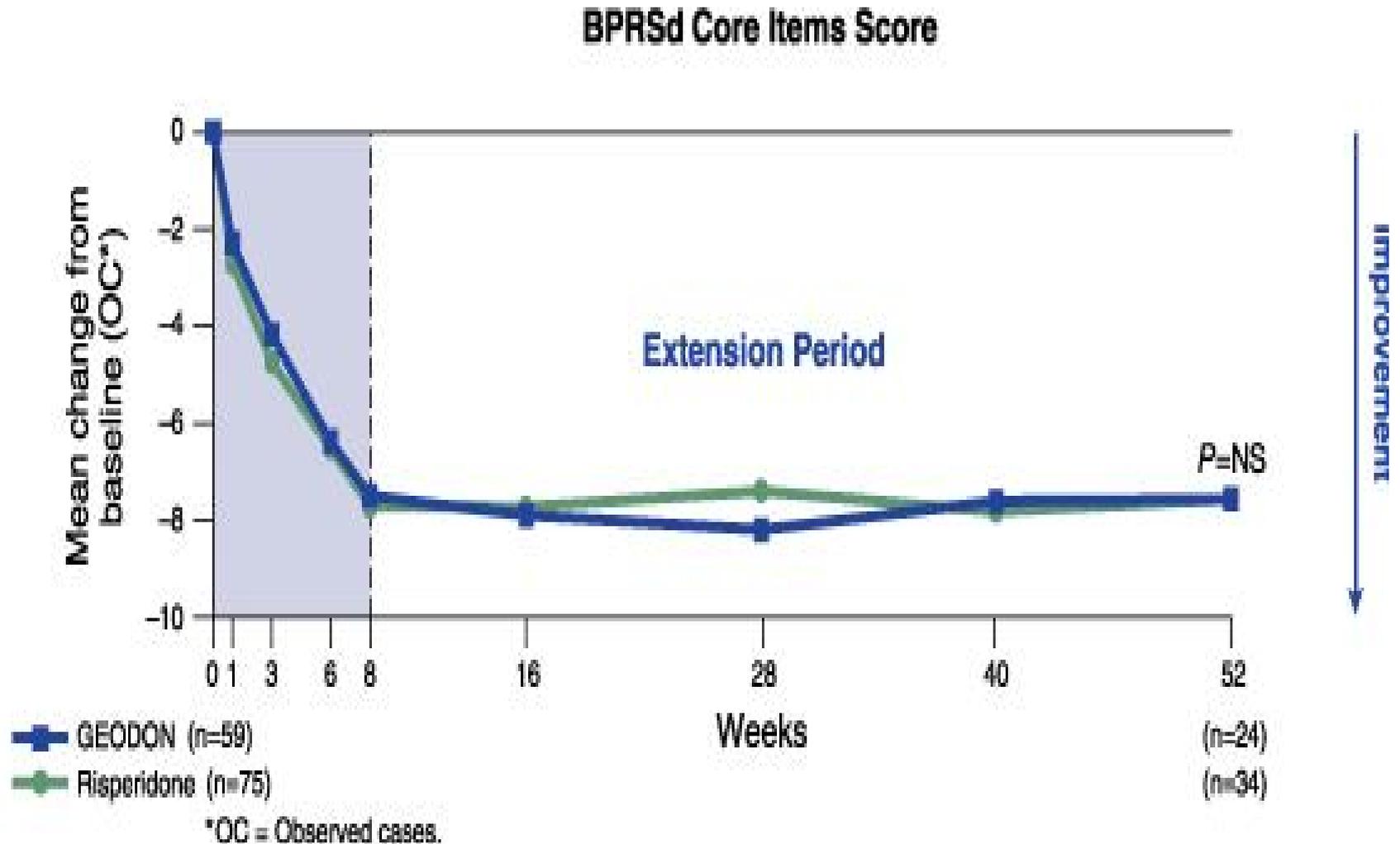
Body System	Patients Receiving Ziprasidone (N=136) <sup>a</sup>		Patients Receiving Olanzapine (N=133) <sup>a</sup>	
	N	%	N	%
Body as a whole	52	38.2	39	29.3
Cardiovascular	7	5.1	10	7.5
Digestive	55	40.4	41	30.8
Endocrine	1	0.7	0	0.0
Hematic and lymphatic	3	2.2	5	3.8
Metabolic and nutritional	5	3.7	14	10.5
Musculoskeletal	8	5.9	8	6.0
Nervous	82	60.3	64	48.1
Respiratory	24	17.6	16	12.0
Skin and appendages	14	10.3	10	7.5
Special senses	8	5.9	6	4.5
Urogenital	9	6.6	5	3.8



# BPRSd Core Items Score



# In a double-blind study vs risperidone... GEODON sustained control of positive symptoms at 1 year



# Systematic literature reviews

- are systematic to remove bias in finding and reviewing the literature.

*Experts may underplay controversy or select only supportive evidence*

*Some evidence may be hard to find.*

**A Catalog of FDA Approved Drug Products**

- Approved and tentatively approved prescription, over-the-counter, and discontinued drugs
- Drug approval letters, labels, and review packages

**Search by Drug Name or Active Ingredient**

Enter at least three characters:

**Browse by Drug Name**

<a href="#">A</a>	<a href="#">B</a>	<a href="#">C</a>	<a href="#">D</a>	<a href="#">E</a>	<a href="#">F</a>	<a href="#">G</a>	<a href="#">H</a>	<a href="#">I</a>
<a href="#">J</a>	<a href="#">K</a>	<a href="#">L</a>	<a href="#">M</a>	<a href="#">N</a>	<a href="#">O</a>	<a href="#">P</a>	<a href="#">Q</a>	<a href="#">R</a>
<a href="#">S</a>	<a href="#">T</a>	<a href="#">U</a>	<a href="#">V</a>	<a href="#">W</a>	<a href="#">X</a>	<a href="#">Y</a>	<a href="#">Z</a>	<a href="#">0-9</a>

**Advanced Search**

- Application Number (NDA, ANDA, BLA)
- Action Dates of Application Approvals and Supplements

**Downloadable Database File **New!!****

[Disclaimer](#)

[CDER Home Page](#) | [CDER Site Info](#) | [Contact CDER](#) | [What's New @ CDER](#)

[FDA Home Page](#) | [Search FDA Site](#) | [FDA A-Z Index](#) | [Contact FDA](#) | [Privacy](#) | [Accessibility](#) | [HHS Home Page](#)

# Included Drugs

Clozapine	not posted
risperidone (1993)	not posted
olanzapine (1996)	not posted
quetiapine (1997)	not posted
ziprasidone (2001)	posted
aripiprazole (2002)	posted

# Trial 114

The medical review team requested additional analyses which excluded data obtained from [redacted]. This reviewer performed the ITT LOCF analyses after excluding patients enrolled by [redacted]. Statistical significance (consistent with the sponsor's report submitted on 6/6/97) for the 80 mg still held, but statistical significance for the 40 mg disappeared for all five primary endpoints (PANSS total,  $p=.103$ ; PANSS negative,  $p=.079$ ; BPRS total,  $p=.097$ ; BPRS core,  $p=.095$ ; and CGI-S,  $p=.076$ ).

## **HIGH DROPOUT RATES**

The 80 mg group had the smallest early discontinuation rate (36%) compared to the 40 mg group (49%) and the placebo group (51%). The dropout rate in the 80 mg group was consistently lower during the entire double-blind treatment period (see Figure 1.1S).

# “EBM 1”

To implement EBM 1, medical schools and other entities implemented training in “critical appraisal.”

# JAMA series “User’s Guide to the Medical Literature”

- Are the Results of the Study Valid?
  - ⑩ Was the assignment of patients to treatment randomized?
  - ⑩ Were all patients who entered the trial properly accounted for and attributed at its conclusion?

⑩ . . . .

**Dec 1, 1993 JAMA**

- What Were the Results?
- Will the Results Help Me in Caring for My Patients?

# “EBM 1”

EBM tends to encourage us to rely on the published literature because it is peer reviewed.

Consequently, traditional systematic reviews, a key tool in evidence-based medicine, often rely on published articles that do not adequately represent all of the relevant information about treatment alternatives.



# YODA Project

## Yale University Open Data Access (YODA) Project

### **A New Approach to Evaluation and Transparency**

Each day, patients and their physicians make treatment decisions with access to only a fraction of the relevant clinical research data. Many clinical studies, including randomized clinical trials, are never published in the biomedical literature. The Yale University Open Data Access project has developed a model to facilitate access to patient-level clinical research data to promote wider availability of clinical trial data and independent analysis by external investigators.

The YODA Project model provides a means for rigorous and objective evaluation of clinical trial data to ensure that patients and physicians possess all necessary information about a drug or device when making treatment decisions. This process includes both coordinating independent examinations of all relevant product data by two separate qualified research groups and making all patient-level clinical research data available for analysis by other external investigators. The model is designed to provide industry with confidence that the analyses will be scientifically rigorous, objective and fair.

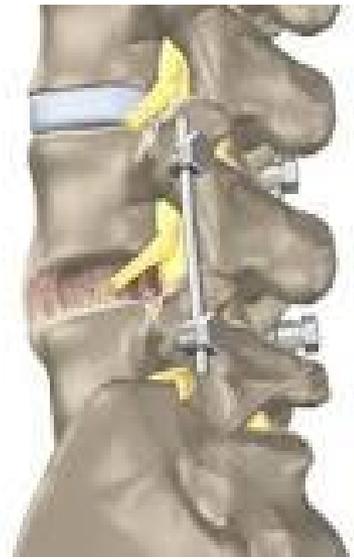
# How We Got Here

- Medtronic's **INFUSE Bone Graft (Recombinant Human Bone Morphogenetic Protein-2) + LT Cage**: approved for anterior lumbar interbody fusion
- **Widely used off-label.**
- **Few or no adverse events were reported in journal publications of Medtronic sponsored trials.**
- **Other studies report more or increased adverse events.**

Medtronic contracted Yale University which subcontracted 2 independent review groups to analyze the evidence.

We were one of two review groups

Annals of internal medicine, June 18, 2013



# Documents and datasets from Yale

- **A total of 17 trials, n = 2090, 4 single-arm**
- **Documents for each trial (> 5 feet)**
  - trial protocol, CT imaging protocol, statistical considerations
  - Final report(s), antibody report
    - The final reports included individual patient case history for adverse event
- **Individual patient data (IPD) for each trial**
  - Raw data
  - Derived data

# Documents and datasets from Yale

- **Documents for 1016 Medwatch online reporting (MDR) forms.**
  - Obtained from two different systems: Global complaint handling (GCH) and Enterprise Product Comment Reporting (EPCR).
  - Include only complaints that resulted in the submission of Documents for 1016 Medwatch online reporting (MDR) forms.
- **Cancer reports**

# Distribution of 174 Studies

Location	RCT	Cohort	Intervention Series	Case Series/ Case Report
<b>Lumbar Spine</b>	<b>11</b>	<b>21</b>	<b>32</b>	<b>15</b>
Tibia	4	2	8	0
Face	7	2	18	5
<b>Other Spine</b>	<b>1</b>	<b>7</b>	<b>16</b>	<b>5</b>
All Others	2	2	12	4
<b>Total</b>	<b>25</b>	<b>34</b>	<b>86</b>	<b>29</b>

# Effectiveness

- rhBMP-2 and iliac crest bone graft had similar outcomes.
- Journal articles made it seem that rhBMP-2 had better fusion rates or functional outcomes
  - “Overall success” (primary outcome) often not reported
  - Stressed favorable numbers even when they weren’t statistically significant
  - Multiple publications
  - Publication and citation of a paper about one particular site not representative of overall findings
  - Nutty “pooled analysis”

# Harms

- Failed to mention stopping one trial for safety concerns
- Reported one adverse event, retrograde ejaculation, for the whole study instead of by treatment group
- There were more cancers in the rhBMP-2 groups
- Adverse events described as “no unanticipated adverse events attributable to rhBMP-2”

# Adverse events

**Comparison of reported adverse events in the published trials versus adverse events in the IPD at 24 months**

Author Trial Study number	Patients, <i>n</i>		Number of AE reported by published study		Number of AE based on IPD*	
	rhBMP-2	Control	rhBMP-2	Control	rhBMP-2	Control
<b>ALIF</b>						
Boden, 2000 INFUSE®/LT-CAGE® Pilot (Study 1)	11	3	6 (1 ileus and delay in gait training, 1 wound dehiscence, 1 low back pain and 3 trauma)	2 (1 ileus and delay in gait training, 1 urinary retention)	20	7
Burkus, 2002 INFUSE®/LT-CAGE® Open Pivotal (Study 2)	143	136	6 (6 intraoperative vascular)†	13 (5 intraoperative vascular, 8 graft side related)	315	274
Burkus, 2002 INFUSE®/ Bone Dowel Pilot (Study 4)	24	22	0	0	40	24
Burkus, 2005‡ INFUSE®/ Bone Dowel Pivotal (Study 5)	55	30	0	0	95	76
Gornet, 2011 MAVERICK™ Disc Pivotal§ (Study 10)	172	405	407, complete reporting of AE in a supplemental table	982, complete reporting of AE in a supplemental table	449	1139

# Conclusion on rhBMP-2

- Journal articles overstated benefits and minimized harms.
- Clues in the early studies were not followed up.
- Many surgeons believed promotional material and the peer reviewed literature, even though it contradicted the FDA's findings.

# Antecedents

- **2004** ClinicalTrials.gov (Vioxx, antidepressants and suicidal thoughts in children)

# Rofecoxib (Vioxx)

- Voluntarily pulled from the market in 2004
- IPD analysis of completed placebo-controlled RCTs for risk of cardiovascular thromboembolic adverse events or any investigator-reported death from any cause:

Year	RR (95% CI)	p-value
2000	2.18 (0.93, 5.81)	0.07
2001	1.35 (1.00, 1.96)	0.05
2002	1.39 (1.07, 1.80)	0.02
2004	1.43 (1.16, 1.76)	<0.001

## Members of Congress blast FDA, drug makers

Friday, September 10, 2004 Posted: 10:49 AM EDT (1449 GMT)

**WASHINGTON (AP) -- Drug manufacturers acknowledge they face a crisis of credibility that they hope to remedy by releasing information about their clinical trials in multiple locations.**

But at a contentious congressional hearing Thursday, representatives of the companies said they also are concerned that releasing all of the information will be so unwieldy that it could confuse doctors and patients.

Dr. John R. Hayes, product team leader at Eli Lilly and Co., said a single report about a drug can number more than 400,000 pages.

Flooding a Web site with 120,000 clinical trials may dilute the usefulness of the information, said Dr. David Wheadon, senior vice president of regulatory affairs for Philadelphia-based GlaxoSmithKline.

### RELATED

- [Drug industry site to summarize select drug trials](#)
- [FDA to warn over kids-antidepressants](#)
- [Study: Talk and pills best for depression in kids](#)

### HEALTH LIBRARY

 [Mayo Clinic](#)

- [Health Library](#)

### YOUR E-MAIL ALERTS

- Food and Drug Administration (FDA)

Search Jobs MORE OPT

Enter Keywords

Enter City

ALL

careerbuilder.com

SEARCH

September  
Posted: 10:49 AM EDT (1449 GMT)

- U.S.
- Weather
- Business at CNNMONEY
- Sports at SI.com
- Politics
- Law
- Technology
- Science & Space
- Health**
- Entertainment
- Travel
- Education
- Special Reports

### SERVICES

- Video
- E-mail Newsletters
- Your E-mail Alerts
- CNNtoGO
- Contact Us

### SEARCH

Web  CNN.com

Search Powered by **YAHOO!** search

# Antecedents

- **2004** ClinicalTrials.gov (Vioxx, antidepressants and suicidal thoughts in children)
- **2008** Selective Publication of Antidepressant Trials and Its Influence on Apparent Efficacy
- **2010** Neurontin settlement

# Neurontin Settlement (2004)

“I recommend that the documents reviewed by me (including sealed documents) and other expert witnesses in the case be made publicly available for the education of the public, students, clinicians, payers and other decision-makers, as well as scholarly work that can be used to guide future understanding of and potential change in how drugs are marketed and used.”

*Dickersin expert report p18 available at*  
<http://dida.library.ucsf.edu/>

# Traditional Publication Bias

- Trying to publish but can't
- Trying to publish but it takes longer (Time lag bias)
- Multiple publication bias
- Location bias
- Language bias
- Citation bias

# Newer types of Reporting bias

- Deliberately preventing or delaying publication or public disclosure
- Selective outcome reporting
- Selective analysis
- Selective pooling bias
- Ghost and guest authorship
- Reframing and spin
- “Publication strategy”
- Subverting the peer review process (Sperell)

# Implications for Systematic Reviews

- Make every effort to find detectable publication and reporting bias
- Even when FDA records are available, additional information from internal correspondence (available from court documents) changes the interpretation of published evidence.
- This means there is an additional level of uncertainty not accounted for in systematic reviews.

# Impact on systematic reviewers

"The reality is that a deliberate fraud is extremely difficult to unearth. If scientists and companies agree to report results in a way that wasn't initially intended, unless you have access to original documents, it is extremely difficult to actually figure out what happened and how it happened," said Dr. Steven Nissen, chairman of cardiovascular medicine at the Cleveland Clinic Foundation in Ohio. "How many other examples like this are there out there that we simply don't know about? That's what's frightening."

# From EBM 1

## From

- Are the Results of the Study Valid?
  - ⑩ Was the assignment of patients to treatment randomized?
  - ⑩ Were all patients who entered the trial properly accounted for and attributed at its conclusion?
  - ⑩ ....
- What Were the Results?

## ...to EBM 2

1. “What additional research do I need to see to weigh the benefits and risks of this drug versus alternatives?”
2. “How do I advocate for patient-centered comparative studies that answer (rather than evade) important questions?”
3. “How do I take a stand that such evidence must be produced before I will adopt an unproven practice on the basis of its “value proposition”?”