

Those with have the gold make the evidence: the pharmaceutical industry and clinical trials

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Points to Cover

- Who funds clinical trials
- Funding and trial outcomes
- How trials can be biased by for-profit funders
- How to tackle the problem of biases

The Willie Sutton Rule

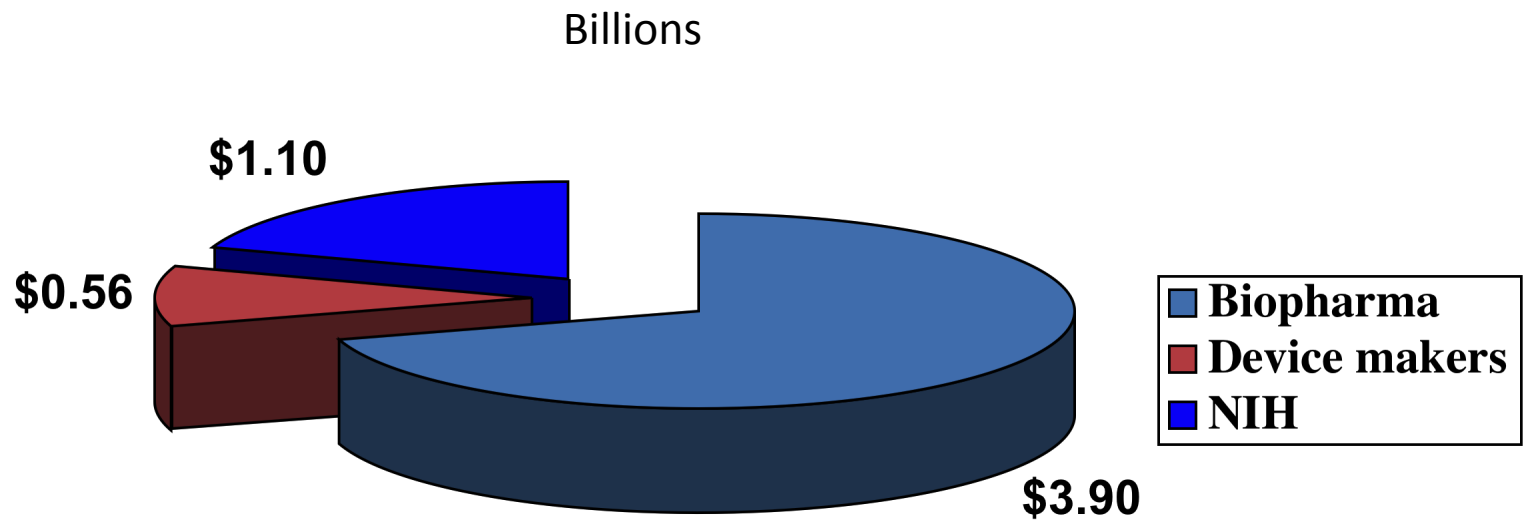


Willie Sutton

Why did he rob
banks?

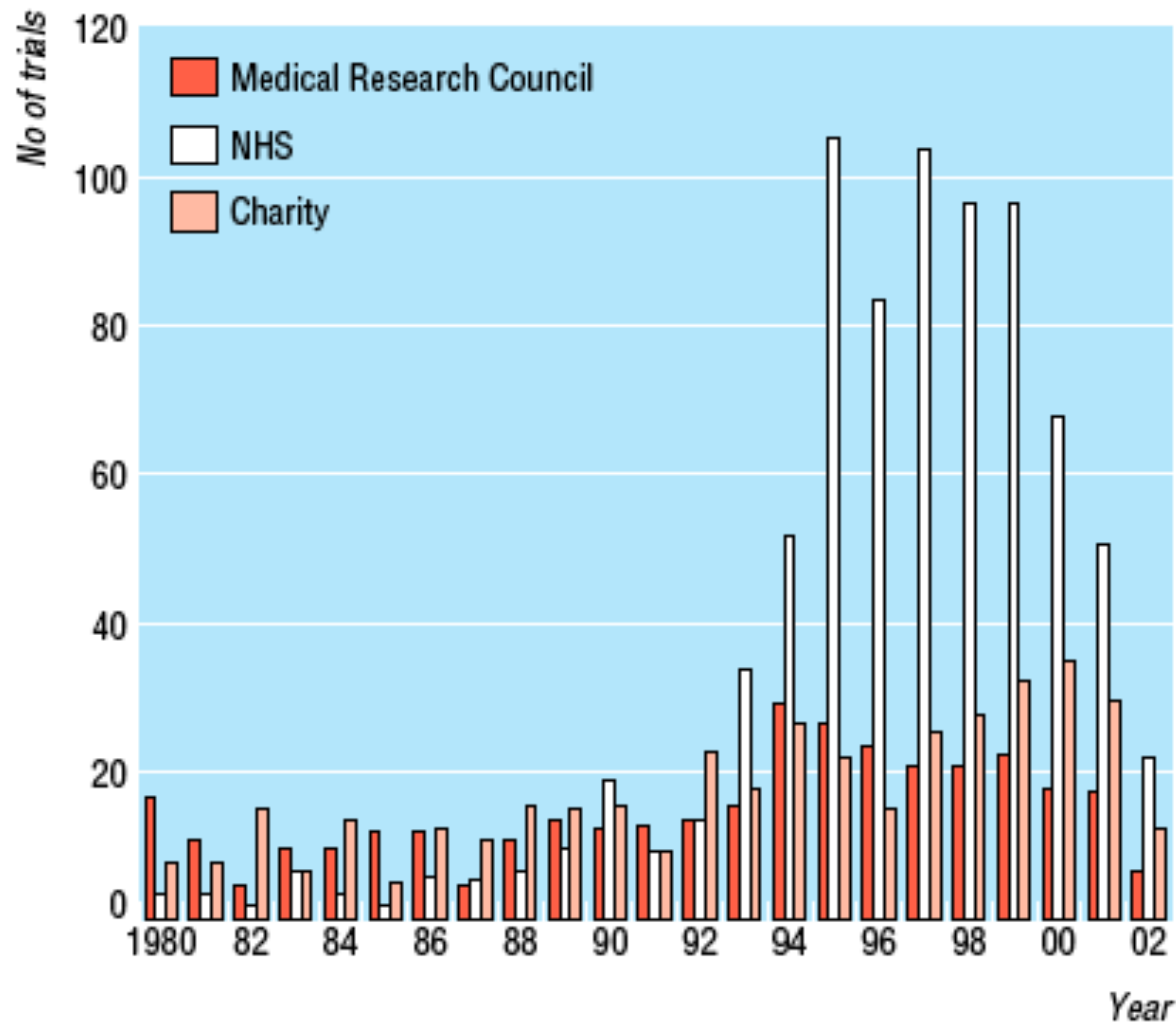
“That’s where the
money is”

Funding for Clinical Research, United States, 2002



CenterWatch 2003

Fewer Non-Industry Funded Trials in the UK



Chalmers et al. BMJ 2003;
327:1017-20

Trial Sponsorship in Norway

Year	No. of pharmacotherapy projects/trials	Percent industry sponsored
1988-1990	670	79
1997	295	68
2000	254	72.8
2004	235	78.7

Hole et al. Eur J Clin Pharm 2001;56:851-3; Winther et al. Eur J Clin Pharm 2007;63: 909-12

Research Results and Funding, 2003 - 2009

Type of research	Results favour industry	Results do not favour industry
Clinical trials	17	3
Pharmaco-economic studies	5	0
Meta-analyses	3	0

Source of Support and Choice of Research Topic

	Industry support		No industry support	
	1985 (%)	1994/5 (%)	1985 (%)	1994/5 (%)
Choice of research topic influenced by commercial application	30	35	7	14

Blumenthal et al. Science 1986;232:1361-6

Blumenthal et al. NEJM 1996;335:1734-9

Sharing of Research Results

Faculty with industrial support

- 11.1% refused to share research results or biomaterials

Faculty without industrial support

- 5.8% refused to share research results or biomaterials

Blumenthal et al. NEJM 1996;335:1734-9

Surfaxin and Latin America

- Discovery Laboratories, Doylestown PA
- Synthetic surfactant (Surfaxin)
- 4 surfactants already on market (first in 1990)
- Associated with 34% relative reduction in neonatal mortality
 - “Without doubt the most thoroughly studied new therapy in neonatal care” (NEJM)

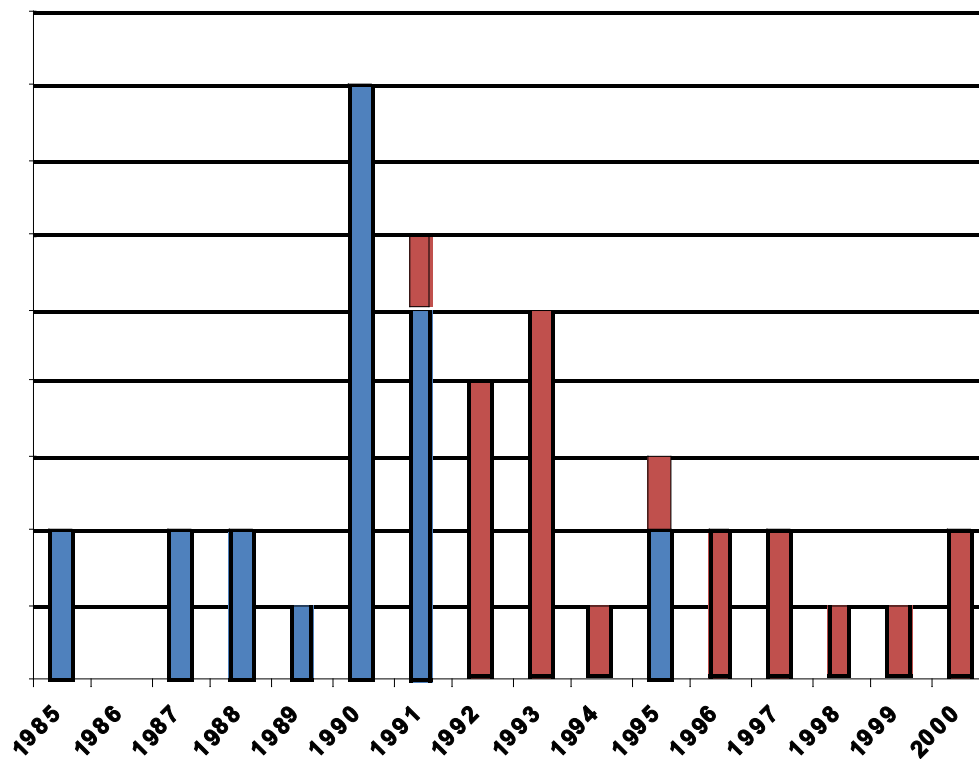
Surfaxin and Latin America

- “Further placebo controlled trials of synthetic surfactant are no longer warranted” (Cochrane Collaboration)
- FDA: “Conduct of a placebo controlled surfactant trial for premature infants with RDS is considered unethical in the USA”
- European trial: Surfaxin vs. approved surfactant

Surfaxin and Latin America

- Proposed locations for study: Mexico, Peru, Bolivia, Ecuador
- Design: Surfaxin vs placebo (vs approved surfactant in some settings)

Trials of Natural and Synthetic Surfactant: 1985-2000



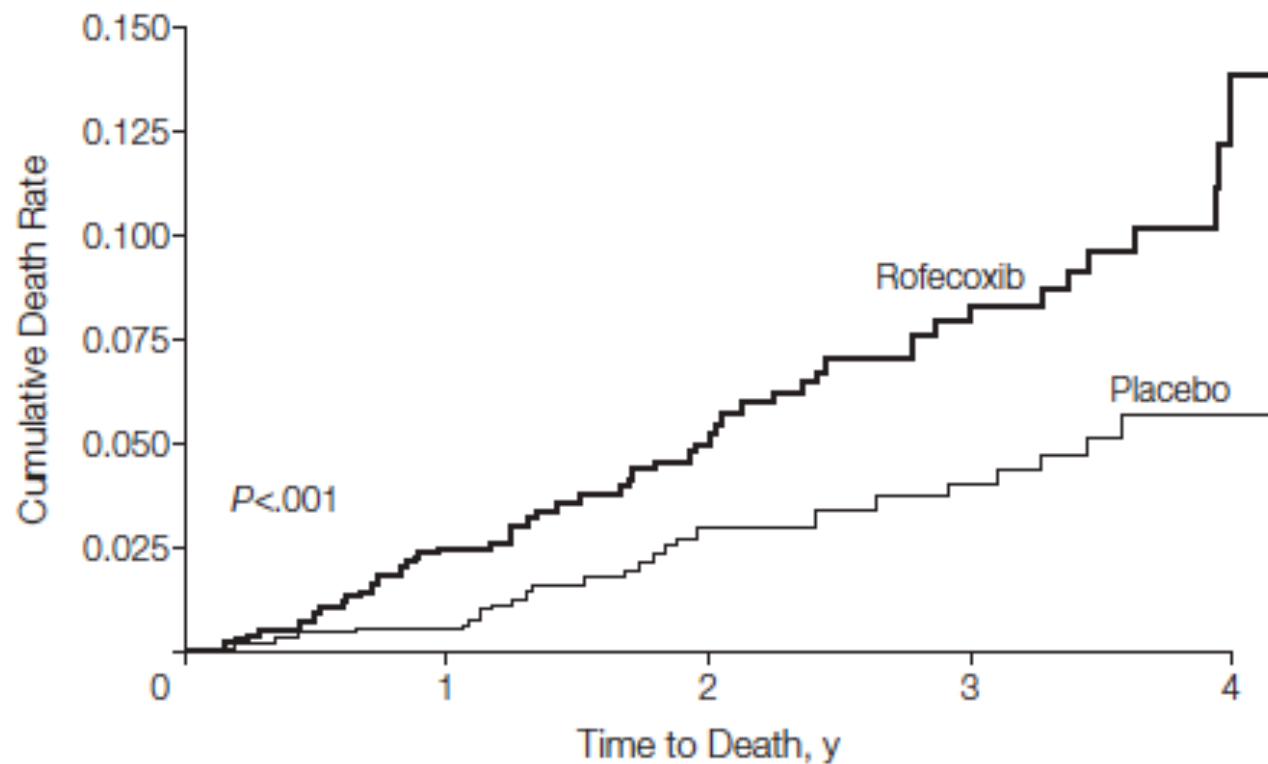
After 1992 only 2 trials against placebo

Merck, Rofecoxib & Alzheimers

- Internal company data April 2001 from 2 Vioxx trials
 - Significant increase in total mortality compared to placebo
 - Information submitted to the FDA in July 2001 used on-treatment analysis that minimized the appearance of any mortality risk
 - December 2001, FDA raised safety questions & Merck responded that the rofecoxib placebo findings are “small numeric differences ... most consistent with chance fluctuations”

Rofecoxib vs. Placebo

Figure. Cumulative Mortality Rate by Treatment in the Alzheimer Disease Studies



Publication Bias

Publication of trials submitted to Swedish regulatory authorities for anti-depressants

- Studies showing significant differences between efficacy of drug and placebo 3 times 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

Lack of Publication - SSRIs & Childhood Depression

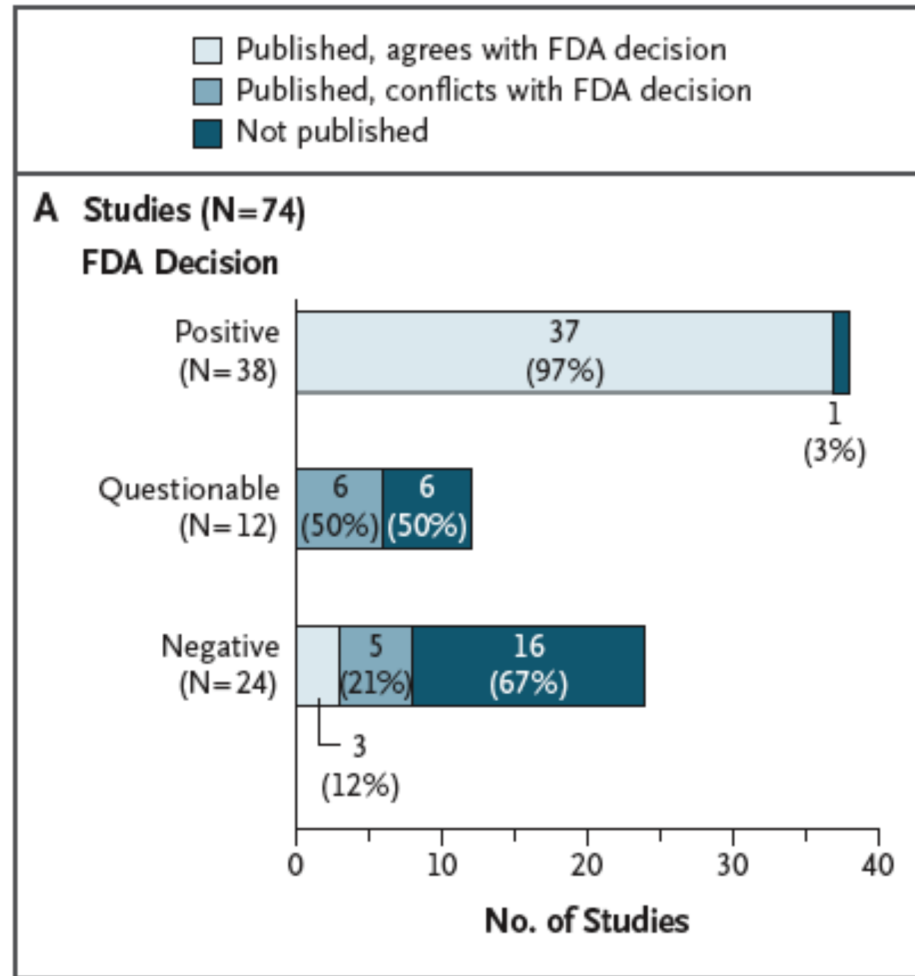
Published data for
paroxetine, sertraline,
venlafaxine

- Some evidence of efficacy
- Little or no evidence of harm

Combined published
and unpublished data
for paroxetine, sertraline,
venlafaxine, citalopram

- Not efficacious
- Small possible risk of suicidal ideation and/or serious adverse events

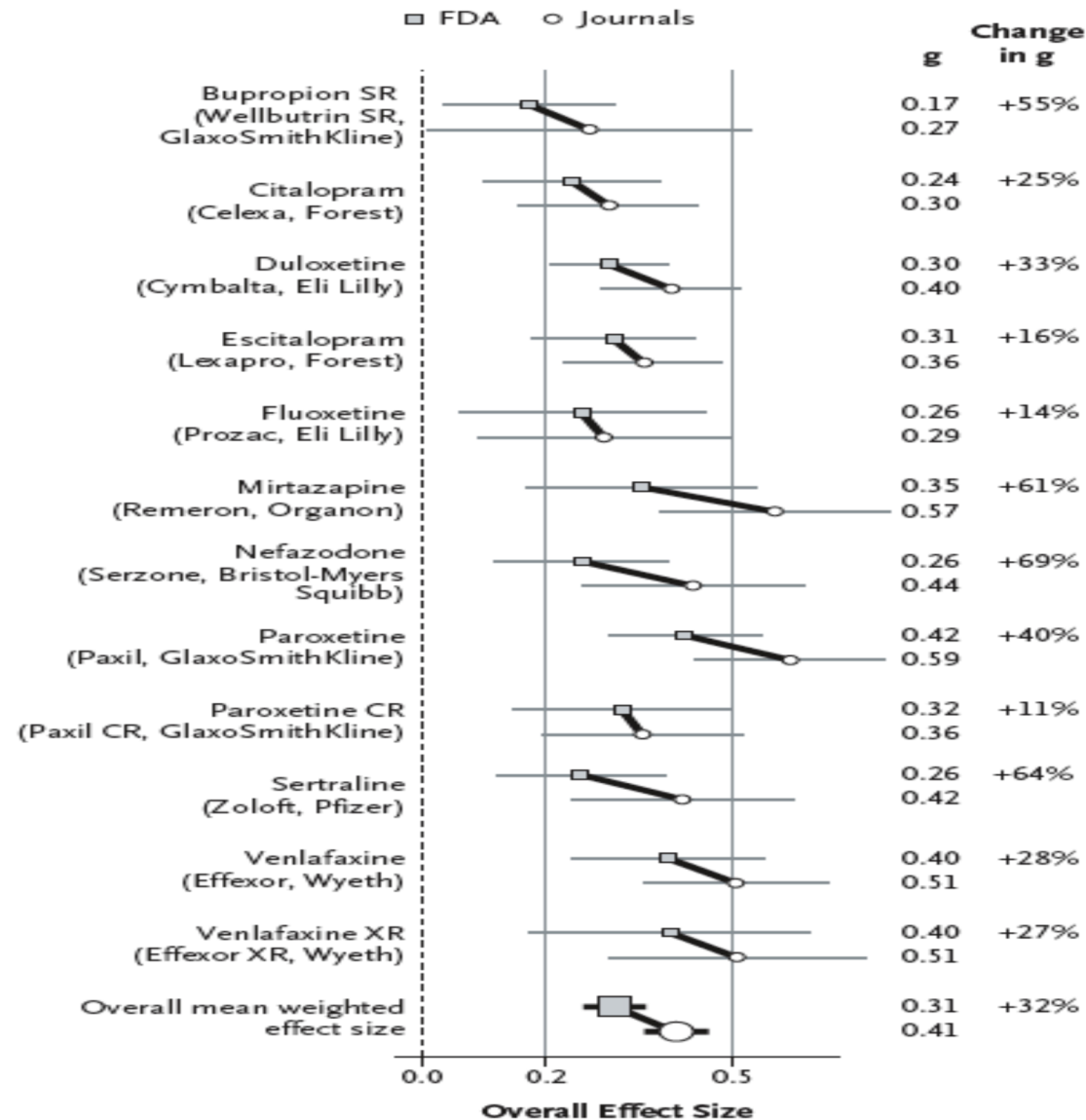
Changing Conclusions in Antidepressant Trials - US



Turner et al. NEJM 2008;358:252-60

Change in Effect Size – Antidepressant Trials

B Overall Effect Size



How Conclusions Change

Table 5. Numbers of Trials with Concordance or Changes in Reporting of Conclusion from NDA to Publication

Conclusion in Paper	Conclusion in NDA				Total for Paper
	Favor Test Drug	Neutral	Favor Comparator	Unknown	
Favor test drug	89	5	4	25	123
Neutral	0	1	0	2	3
Favor comparator	0	0	0	0	0
Unknown	0	0	0	0	0
Total for NDA	89	6	4	27	126

Comparison between conclusions in efficacy trials in NDAs for approved NMEs submitted to FDA in 2001-02 and conclusions in publications

In addition after 5 years 22% of trials not published

Rising et al. PLoS Medicine 2008;5(11):e217

WORLDWIDE PUBLICATIONS
STATUS UPDATE

ZOLOFT[®]
(Sertraline HCl)

PREPARED BY
CURRENT MEDICAL DIRECTIONS, INC
JANUARY 29, 1999

Prepared by Current Medical Directions, Inc.

ANXIETY

POST-TRAUMATIC STRESS DISORDER

Author—Title	Vendor	Status
Author TBD—(640) Sertraline vs. placebo in PTSD	Paladin	Poster presented at ECNP, 1997. Paper is completed, but revisions are needed.
Author TBD—(671) Title TBD	Paladin	Poster presented at ECNP, 1998. First draft completed, but additional analyses needed. Both 640 and 671 studies to be submitted soon. One will go to <i>New England Journal of Medicine</i> and the other to <i>JAMA</i> .

Ghostwriting - Articles on Paroxetine

	Source of article	
	Current Medical Directions (Ghostwritten)	Other (Not ghostwritten)
Medline listing per author	70	37
Literature profile per article	1839	283
Citation rate of series	20.2	7.7

Healy et al. British Journal of Psychiatry 2003;183:22-7

October 1998

SEROXAT/PAXIL
ADOLESCENT DEPRESSION
Position piece on the phase III clinical studies

EXECUTIVE SUMMARY

Results from the 2 placebo-controlled, phase III clinical trials designed to assess the efficacy and safety of Seroxat/Paxil in adolescents with major depression are now available.

Study 329 (conducted in the US) showed trends in efficacy in favour of Seroxat/Paxil across all indices of depression. However, the study failed to demonstrate a statistically significant difference from placebo on the primary efficacy measures. The second study (study 377), which was conducted in Europe, South America, South Africa and the United Arab Emirates, showed a high placebo response rate and failed demonstrate any separation of Seroxat/Paxil from placebo.

Data from these 2 studies are insufficiently robust to support a label change and will therefore not be submitted to the regulatory authorities. Results from Study 329 will be presented in abstract form at the ECNP meeting (Paris, November 1999) and a full manuscript will be progressed. There are no plans to publish data from Study 377.

“Study 329 ... showed trends in efficacy”

The second study ... failed demonstrate any separation of Seroxat/Paxil from placebo

Data from these 2 studies ... will therefore not be submitted to the regulatory authorities

TARGET

To effectively manage the dissemination of these data in order to minimise any potential negative commercial impact.

i) regulatory agencies would not approve a statement indicating that there are no safety issues in adolescents, as this could be seen as promoting off-label use

ii) it would be commercially unacceptable to include a statement that efficacy had not been demonstrated, as this would undermine the profile of paroxetine.

- Positive data from Study 329 will be published in abstract form at the ECNP (Paris, November 1998) and a full manuscript of the 329 data will be progressed.

And GSK Gagged Researchers

“Those researchers, including myself, who *did* see results of negative paroxetine industry trials were prohibited by nondisclosure contracts from discussing them.”

Jane Garland MD
Pediatric Psychiatrist
Vancouver

Garland. CMAJ 2004;170:489-91

Stopping Trials for Commercial Reasons

Trial Name	Drug	Company
CONVINCE	Verapamil	G.D.Searle/Monsanto/ Pharmacia
ICON3	Paclitaxel	BristolMyers Squibb
	Aminoguanidine	Hoechst Marion Roussel
	Liposomal doxorubi cin	Pfizer & Liposome Co.
PROTECT	Diltiazem	Hoechst Marion Roussel
	Fluvastatin	Novartis
	Intravenous Immunoglobulin	Sandoz India

Reasons for Terminating Clinical Trials

- Reasons why research terminated four years or more after IND (Investigational New Drug) filing, 1980-4:
 - Economics 43%
 - Efficacy 31%
 - Safety 21%

Seeding Trials

Executive at Contract Research Organization:

“We have been approached by several pharmaceutical manufacturers to conduct ‘seed’ studies. These studies are usually intended to increase the use of the manufacturer’s product and sometimes lack scientific integrity...The intent is to influence physician and patient behavior”

Seeding Trials - ADVANTAGE

- Comparison of GI tolerability and effectiveness of Vioxx and Naproxen
- Funded by Merck
- “The trial was designed by Merck’s marketing division to fulfill a marketing objective; Merck’s marketing division handled both the scientific and the marketing data, including collection, analysis, and dissemination; and Merck hid the marketing nature of the trial from participants, physician investigators, and institutional review board members”

Economics

- Alan Maynard (British health economist):
 - “Economic theory predicts that firms will invest in corruption of the evidence base wherever its benefits exceed its costs...Investment in biasing the evidence base, both clinical and economic, in pharmaceuticals is likely to be detailed and comprehensive, covering all aspects of the appraisal process”

Fines & Profits

Company	Drug	Fine (year)	Revenue (years)
Lilly	Olanzapine	\$1.4 billion (2009)	\$36 billion (2000 – 2008)
Pfizer	Gabapentin	\$430 million (2004)	\$2.27 billion (2002)
Pfizer	Valdecoxib & 3 other drugs	\$2.3 billion (2009)	\$16.8 billion (2001 – 2008)

Jail Sentences

John Braithwaite, Corporate Crimes in the Pharmaceutical Industry, 1982 (page 308):

To my amazement, two American executives I interviewed explained that they had held the position of 'vice-president responsible for going to jail'...Lines of accountability had been drawn in the organisation such that if there were a problem and someone's head had to go on the chopping block, it would be that of the 'vice-president responsible for going to jail'.

New Ways of Dealing With the Problem

- Firewall between the funder (drug companies) and those doing and analyzing the trials
 - Companies turn over the money to a third party (e.g., CIHR, NIH) which then calls for tenders to do the research and selects the best candidate
- Public funding of clinical trials
 - Money to do this would come from savings – non-exclusive rights to produce drug sold to multiple companies & competition would lower prices; less patent litigation; less promotion