From scientific evidence to implementation into research and practice

Alessandro Liberati
Italian Cochrane Centre

Xth birthday of the Cochrane Drug and Alcohol Group

THE EFFECTIVENESS OF INTERVENTIONS FOR ADDICTIONS:

THE COCHRANE DRUGS AND ALCOHOL GROUP CONTRIBUTION

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Content of the presentation

- The simplistic expectation of the flow from research to clinical practice
- Why this “simplistic” expectation does not come through?
- What can be done to improve it?
- What are the obstacles?
- Concluding remarks

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The simplistic expectation of the flow between research and clinical practice

The simplistic expectation of the flow between research and clinical practice

- **Research is planned:**
  - considering sistematically what is already known
  - focussing on relevant uncertanties for patients and relevant innovation for health services
  - taking applicability and generalizability into account

- **There is an orderly mechanism:**
  - to incorporate relevant research findings into practice
  - to consider them when choosing alternative models of services configuration

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What's wrong with this logical path?

What's wrong in this logical path?

- Research often does not address relevant questions
  - For patients
  - For health services
- Many studies are poorly conducted and reported
- Information has limited applicability for services configuration and policy making
- Knowledge per se does not shape clinical practice
- Cultural and organisational factors interfere with the implementation of effective practices

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Research often does not address relevant questions For patients

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Two examples

Relation between agendas of the research community and the research consumer

Deborah Tallon, Jiri Chard, Paul Dieppe

The Lancet, 2000

THE RELATION BETWEEN FUNDING BY THE NATIONAL INSTITUTES OF HEALTH AND THE BURDEN OF DISEASE

CARY P. GROSS, M.D., GERARD F. ANDERSON, PH.D., AND NEIL R. POWE, M.D., M.P.H., M.B.A.

N Engl J Med, 1999

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Treatment	Total studies	Randomised controlled trials	Commercially funded	Positive outcome
Alternative and complementary	49 (5%)	29 (59%)	5 (4%)	43 (88%)
Drug (injected)	89 (10%)	50 (56%)	5 (4%)	87 (98%)
Drug (oral)	461 (50%)	330 (72%)	109 (85%)	447 (97%)
Education	33 (3%)	14 (42%)	1 (0·8%)	29 (88%)
Physiotherapy and exercise	60 (6%)	24 (40%)	3 (2%)	55 (92%)
Surgery	238 (26%)	13 (5%)	5 (4%)	215 (90%)
Total	930 (100%)	460 (49%)	128 (100%)	876 (94%)

Table 1: **Summary of results from review of studies on osteoarthritis of the knee**

Treatment	Have not tried	Not helpful	Slightly helpful	Moderately/ extremely helpful	Total responses
Knee replacement	73 (92%)	0	1 (1%)	5 (6%)	79
Tablets*	8 (9%)	6 (7%)	16 (18%)	59 (66%)	89
Injections in the knee	42 (51%)	7 (9%)	10 (12%)	23 (28%)	82
Aids and adaptions	37 (44%)	1 (1%)	22 (26%)	25 (29%)	85
Removal of fluid/debris	50 (63%)	6 (8%)	8 (10%)	15 (19%)	79
Other treatment	14 (58%)	1 (4%)	4 (17%)	5 (21%)	24
Physical therapy	36 (44%)	7 (9%)	19 (23%)	20 (24%)	82
Complementary therapy	57 (72%)	5 (6%)	8 (10%)	9 (11%)	79
Education and advice	40 (49%)	5 (6%)	20 (24%)	17 (21%)	82
No treatment at all	35 (76%)	6 (13%)	4 (9%)	1 (2%)	46

*We used the word tablets in the questionnaire, rather than NSAIDs or analgesics, since focus group discussion suggested some patients do not differentiate between these drug types.

Table 2: **Summary of patients' responses to the question: how helpful do you find these treatments for reducing pain and disability?**

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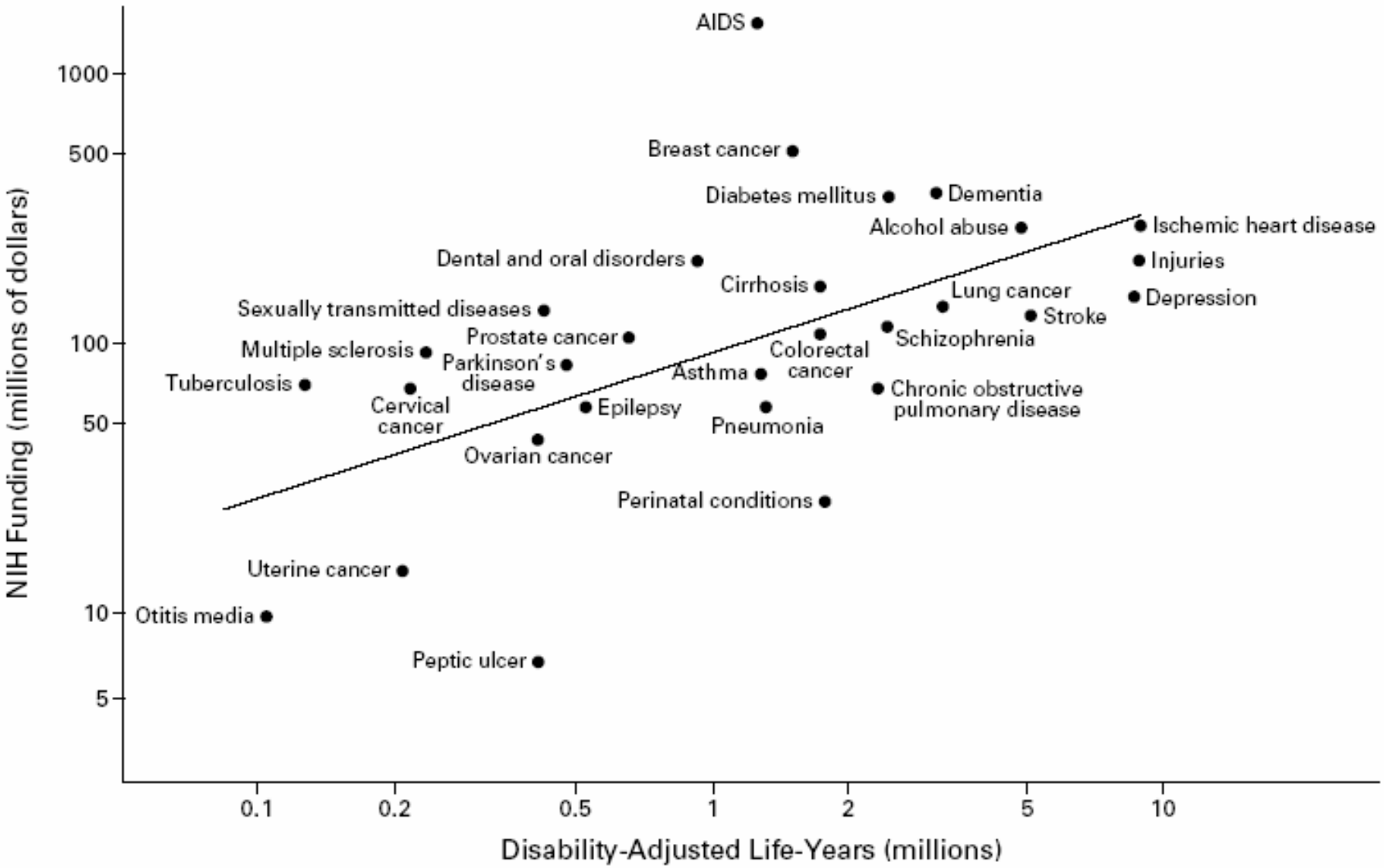

Figure 1. Relation between NIH Disease-Specific Research Funding in 1996 and Disability-Adjusted Life-Years for 29 Conditions in 1990.

The axes are drawn to logarithmic scale. The line represents funding predicted on the basis of a linear regression with disability-adjusted life-years as the explanatory variable. One disability-adjusted life-year is defined as the loss of one year of healthy life to disease.

Information has limited relevance for services' configuration and policy making

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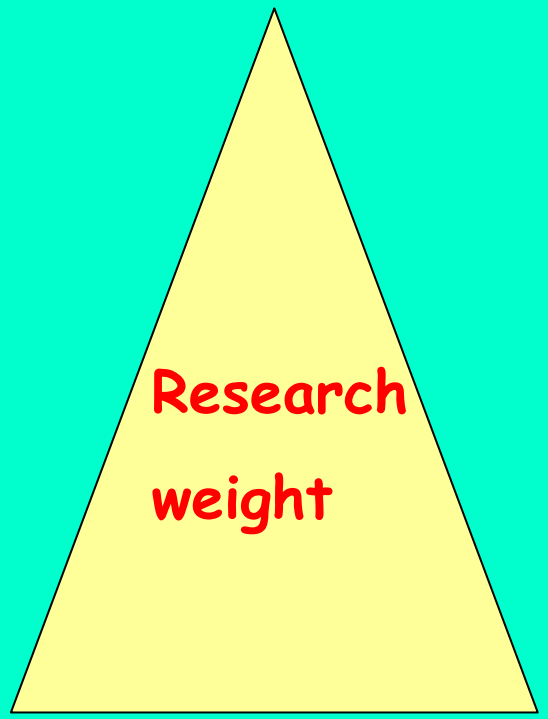
DECISION MAKING IN HEALTH CARE



Macro	Major health policy options
Meso	Administration/Organisation
Micro	Clinical policies

Knowledge per se does not shape clinical practice

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Why Don't Physicians Follow Clinical Practice Guidelines?

A Framework for Improvement

Michael D. Cabana, MD, MPH

Cynthia S. Rand, PhD

Neil R. Powe, MD, MPH, MBA

Albert W. Wu, MD, MPH

Modena H. Wilson, MD, MPH

Paul-André C. Abboud, MD

Haya R. Rubin, MD, PhD

JAMA. 1999;282:1458-1465

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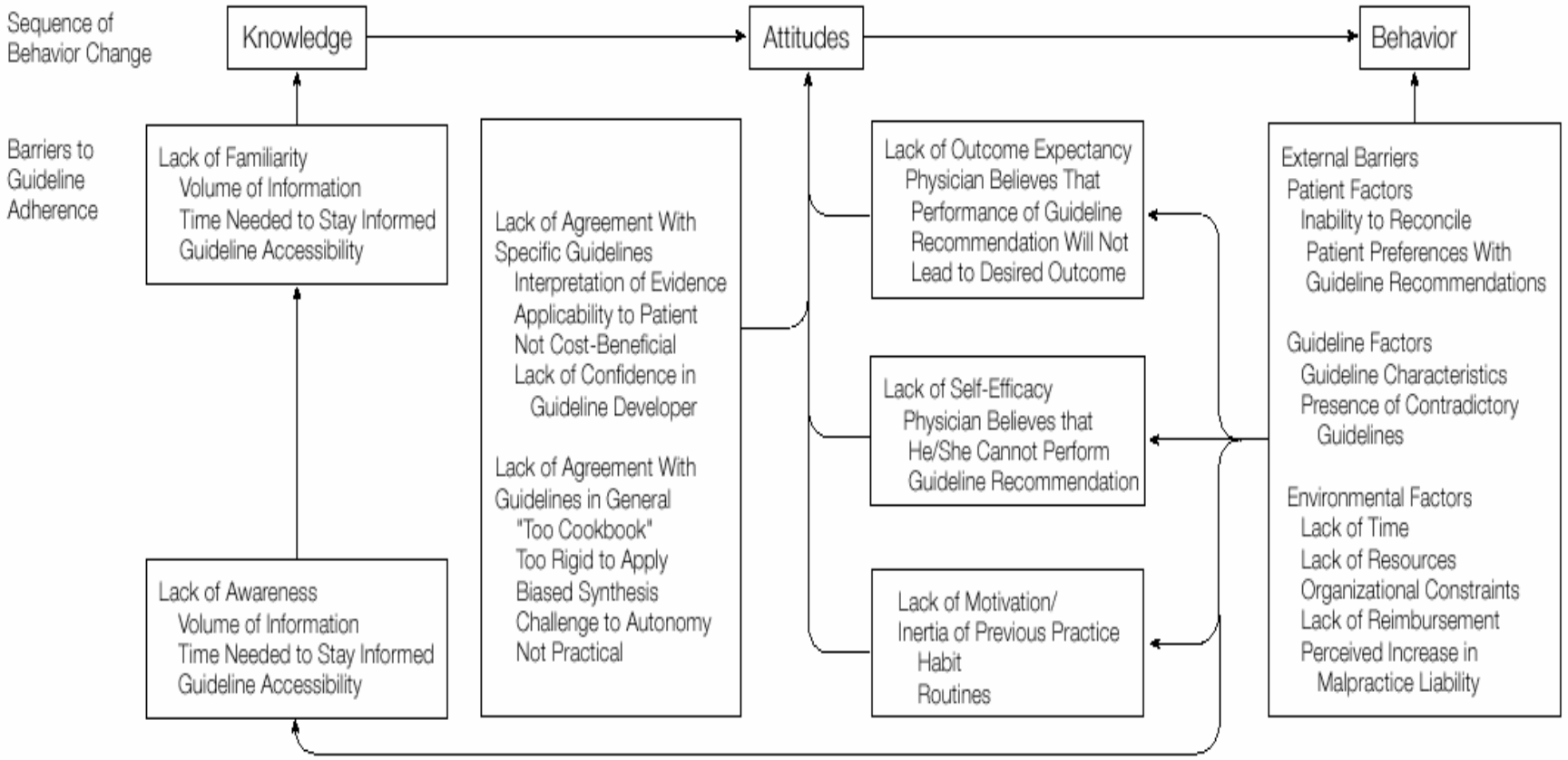
JAMA. 1999;282:1458-1465

Figure. Barriers to Physician Adherence to Practice Guidelines in Relation to Behavior Change



What can we do to improve it?

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What can we do to improve it?

- Understanding the imbalance in the research agenda

- Acting to modify the wastes that occur at different stages of the research process (prioritisation, conduct, publication and dissemination)
- Improving citizens' and patients' awareness
- Limiting commercial over-interference in reseearch

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The imbalance in the research agenda

The risk of bias from omitted research

Evidence must be independently sought and free of economic interests

The rise of evidence based health care has highlighted the use of ineffective interventions, the risks of uncoordinated research, and the consequences of relying on studies published in prestigious journals while ignoring unpublished ones that have negative findings.[1–5] Systematic reviews of the best evidence are now recognised as fundamental tools in overcoming these problems because they highlight questions that need urgent answers.[6] But is evidence based health care achieving its goals? Aren't systematic reviews which are based on existing research at risk of amplifying the irrelevant? Should we be more concerned about "bias caused by omitted research" than the well recognised pitfall of publication bias?

The increasing awareness of this danger is leading to efforts to correct this imbalance. One such attempt is the Cochrane Collaboration (an international organisation named after Archie Cochrane, the British epidemiolo- GISSI trial in Italy as well as by the international studies on infarct survival (ISIS) for the treatment of myocardial infarction should make these trials models in terms of the example they provide of involving doctors and hospitals that are representative of different levels of the healthcare systems.[9 10]

To produce evidence we must work independently, free from prejudice and unfettered by the economic interests at play in medicine. It is unfortunate that the industrialised countries, especially in Europe, have delegated the control of drug trials to pharmaceutical companies. We are not suggesting that the industry is wicked, and we acknowledge its role in providing essential drugs, such as antibiotics, antiulcer agents, antipsychotic drugs, and fibrinolytic agents, to name just a few. Nevertheless, delegating this responsibility places clear limitations on research, and these seem to be growing.

For economic reasons, researchers are drawn to

Garattini S, *Br Med J 2000*

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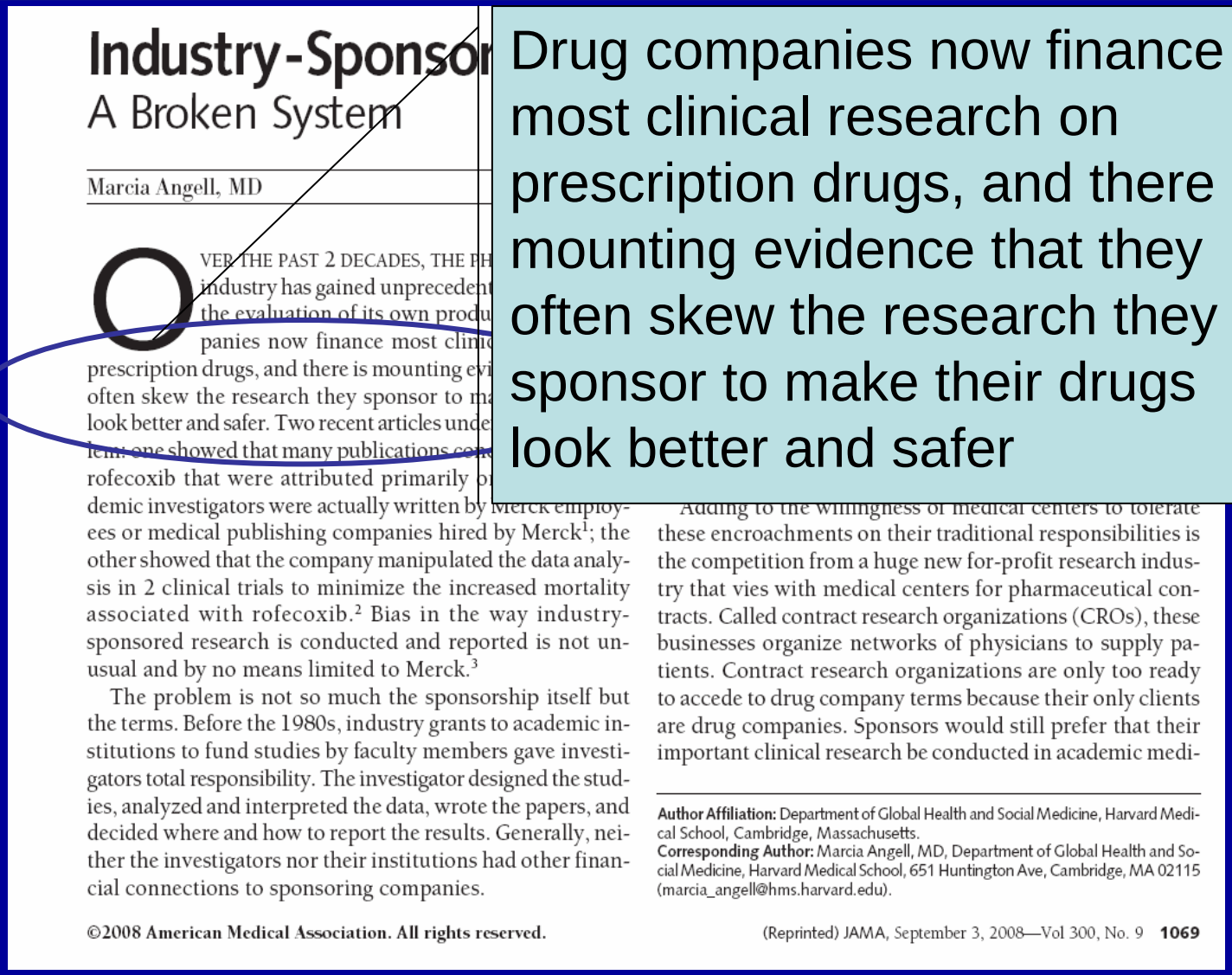
A recent editorial



Industry-Sponsor
A Broken System

Marcia Angell, MD

OVER THE PAST 2 DECADES, THE PH
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rofecoxib that were attributed primarily o
demic investigators were actually written by Merck employees or medical publishing companies hired by Merck[1]; the other showed that the company manipulated the data analysis in 2 clinical trials to minimize the increased mortality associated with rofecoxib.[2] Bias in the way industry-sponsored research is conducted and reported is not unusual and by no means limited to Merck.[3]

The problem is not so much the sponsorship itself but the terms. Before the 1980s, industry grants to academic institutions to fund studies by faculty members gave investigators total responsibility. The investigator designed the studies, analyzed and interpreted the data, wrote the papers, and decided where and how to report the results. Generally, neither the investigators nor their institutions had other financial connections to sponsoring companies.

Adding to the willingness of medical centers to tolerate these encroachments on their traditional responsibilities is the competition from a huge new for-profit research industry that vies with medical centers for pharmaceutical contracts. Called contract research organizations (CROs), these businesses organize networks of physicians to supply patients. Contract research organizations are only too ready to accede to drug company terms because their only clients are drug companies. Sponsors would still prefer that their important clinical research be conducted in academic medi-

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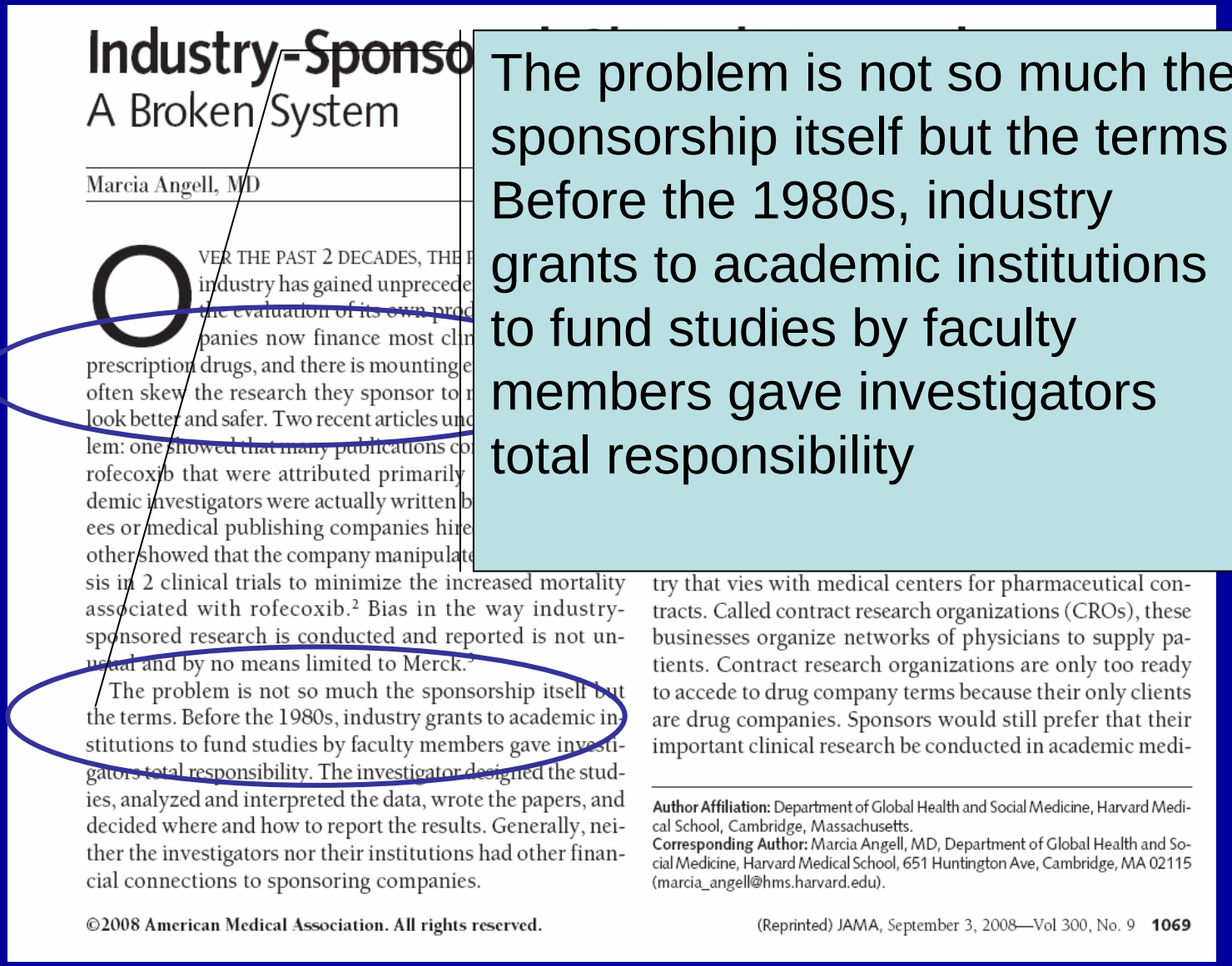
Drug companies now finance most clinical research on prescription drugs, and there is mounting evidence that they often skew the research they sponsor to make their drugs look better and safer

Angell M. JAMA 2008;300:1069-71

A recent editorial



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From support to intrusion:

how does pharma companies support works these days….

……..In recent years, however, sponsoring companies have become intimately involved in all aspects of research on their products……..

……..They often design the studies; perform the analysis; write the papers; and decide whether, when, and in what form to publish the results…….

Angell M. JAMA 2008

What are the obstacles?

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What are the obstacles?

- Lack of awareness that lack of proper research is an important determinant of poor quality care
- Loss of professionals' responsibility
- Lack of structural incentives
- Lack of NHS's funding and support (in Italy, with the noticeable exception of the Italian Drug Agency – AIFA - bid in Italy)
- Limited ability to produce relevant and rapidly usable information

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The good news:
Systematic reviews in the AIFA bid

- **Projects that should be completed in 1 year**
- **Particular attention to produce relevant information for**
  - **Information relevant for regulatory decisions**
  - **Information relevant for the design of new primary studies**
- **46 Letters of intent (out of about 300) in 2008**

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Loss of health professionals' responsibility

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Conflicts of interests and/or lack of interest ???

An hypothetical (??) conversation between
a young (naive?) investigator and a leader of a reseach group

…….The study you are thinking (a head to head comparison of the three drugs that are currently being used in that disease) would be of enormous interest for patients, and would never be supported by pharmaceutical companies…..

However, I see at least two problems:

1) **It is very unlikely that we can succeed in convincing groups that could be potentially interested in such a study to actually undertake it……. most of them are already busy with other studies sponsored by pharmaceutical companies**

2) **I'm afraid that the costs of such a study would be substantial (a few million euros) and therefore it would hard to find public support for it**

I do not see how we could embark in a study like this one that would - on the other hand - put us in a conflicting relationship with pharmaeceutical companies

Concluding remarks

- There is a long way to go before the "*expected logical path*" can become a reality.
- It is important to understand the different determinants of the current situation to identify potential remedies
- The international collaboration is a key element for a better world

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Happy birthday !!!!!

This is an important event to many people

- The Editors of the Group (M. Davoli, R Ali, F Faggiano, M Farrell, D Foxcroft, W Ling)
- The Editorial Team (L Amato, S Vecchi, S Mitrova, S Minozzi)
- People that supported their work in Italy and different part of the world
- People working in the italian NHS and International Organisations and using the information produced by the Cochrane Drug and Alcohol Review Group

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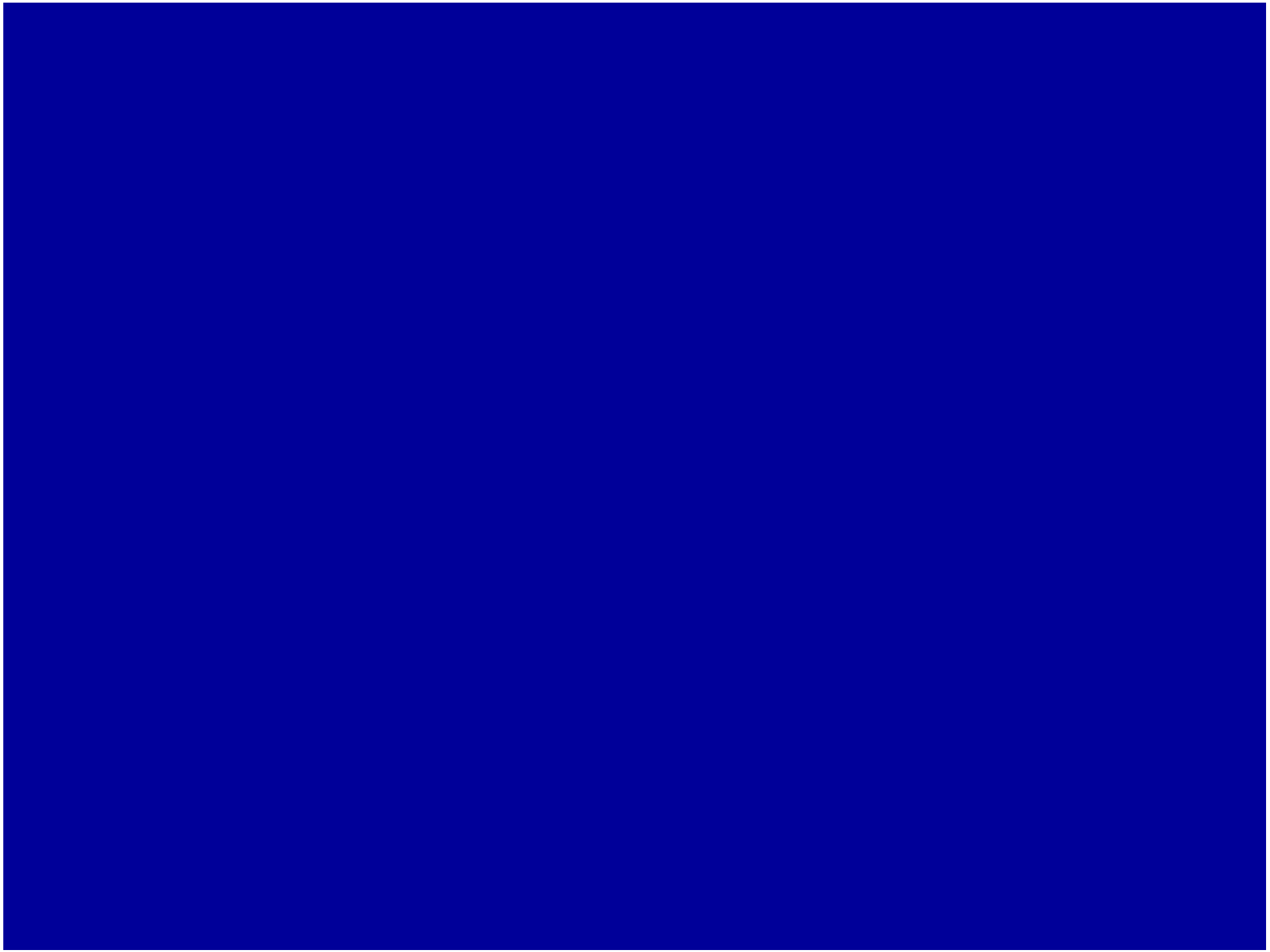

Efficacy, safety, and cost of new anticancer drugs

Silvio Garattini, Vittorio Bertele'

Italian pharmacologists Silvio Garattini and Vittorio Bertele' note that new anticancer drugs reaching the European market in 1995-2000 offered few or no substantial advantages over existing preparations, yet cost several times—in one case 350 times—as much

BMJ 2002, 325, 269

Gli ostacoli

- Ambiente culturale non favorevole
- Doppio standard etico tra ricerca e pratica clinica
- Mancanza della infrastruttura necessaria
- Mancanza di adeguati incentivi
- Conflitti/mancanza di interesse