Ricerca for profit e not-for-profit: una collaborazione (im)possibile?

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Riunione Annuale Nettwork Cochrane Italiano
Come migliorare la qualità e rilevanza della ricerca clinica
Roma, ISS, 15 Novembre 2011

CeVEAS
CENTRO PER LA VALUTAZIONE
DELL'EFFICACIA DELL'ASSISTENZA SANITARIA

SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Unità Sanitaria Locale di Modena

Contenuti della presentazione

- *Financial anatomy of biomedical research*: ovvero alcune considerazioni preliminari sulla *governance* della ricerca profit e not-for-profit
- Cosa abbiamo imparato dagli ultimi 10(-20) anni sugli studi clinici: ruoli di RCT e comparative effectiveness research
- Scenari futuri di collaborazione e un punto di vista dei Comitati Etici
- Conclusioni

Contenuti della presentazione

- Financial anatomy of *biomedical research*: ovvero alcune considerazioni preliminari sulla *governance* della ricerca profit e not-for-profit
- "*biomedical research was defined as the life sciences excluding the agricultural science plus the addition of psychology*"
- Cosa abbiamo imparato dagli ultimi 10(20) anni sugli studi clinici e diversi ruoli per RCT e comparative effectiveness research
- Scenari futuri di collaborazione e un punto di vista dei Comitati Etici
- Conclusioni

Financial anatomy of biomedical research

- Since the Second World War, biomedical research has been the beneficiary of parallel advances in the physical, social, and information sciences.
- That momentum greatly expanded financial support for biological research, especially that related to human health.
- However, not until the early 1980s did total financing for the biomedical sciences exceed that of engineering and the physical sciences

Financial Anatomy of Biomedical Research
Hamilton Moses III, E. Ray Dorsey, David H. M. Matheson, Samuel O. Thier
JAMA. 2005;294(11):1333-1342.

Chi finanzia e sostiene la ricerca biomedica

- Una visione duale, per tesi/antitesi?
  - Profit vs not-for-profit

- Piuttosto, una realtà tetrapartita:
  - Fondi federali/sovranazionali (*federal funding* o europei)
  - Fondi statali e locali (nazionali e regionali)
  - Privato not-for-profit (*Foundations*)
  - Privato/Industria (for profit)

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Chi finanzia e sostiene la ricerca biomedica

- Una realtà tetrapartita
  - Fondi europei (governativi o *federal funding*)
  - Fondi statali e locali (nazionali e regionali)
  - Privato not-for-profit (Fondazioni)
  - Privato/Industria

- Orientata in modo interattivo verso:
  - Ricerca di base vs clinica
  - Enti di ricerca / Università
  - Sistema sanitario … health policy e health services research (nuove aree)
  - … esigenza di approcci più integrati e più multidisciplinari

Financial anatomy of biomedical research

Enhancing research productivity and evaluation of benefit are pressing challenges, **requiring:**

(1) more effective translation of basic scientific knowledge to clinical application;

(2) critical appraisal of rapidly moving scientific areas to guide investment where clinical need is greatest, not only where commercial opportunity is currently perceived; and

(3) more specific information about sources and uses of research funds than is generally available to allow informed investment decisions.

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Migliorare la produttività della ricerca

1. Più efficace traslazione dalla ricerca di base alla applicazione clinica;

2. Quali le aree cliniche più promettenti per orientare gli investimenti (bisogni clinici vs opportunità commerciali)

3. Maggiori informazioni complessive su fonti e usi dei fondi di ricerca per orientare meglio gli investimenti

Financial Anatomy of Biomedical Research
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Migliorare la produttività della ricerca

1. Più efficace traslazione dalla ricerca di base alla applicazione clinica

Ricerca not-for-profit

- Need oriented (existing drugs effectiveness)
- Earlier access to very promising drugs?

Ricerca for profit

- Market oriented
- Is it really single drug oriented?

What can done

Patients and research community higher involvement (proper advocacy role)

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Migliorare la produttività della ricerca

2. aree cliniche più promettenti per orientare gli investimenti (bisogni vs opportunità commerciali)

Ricerca not-for-profit

- Patient-oriented
- Need oriented (quality of care)

Ricerca for profit

- Single drug oriented
- Market oriented

What can done

- Increase comprehensive periodic redefinitions of priorities (every 10 years) with higher participation

- Increase comprehensive periodic redefinitions of priorities (every 10 years) with higher participation

"Today (2010) more than 75% of pharmaceutical drug trials in the US are being conducted by the private sector …"
In Europe it is probably approaching 90% …

Migliorare la produttività della ricerca

3. Informazioni complessive su fonti e usi dei fondi di ricerca per orientare gli investimenti

Ricerca not-for-profit

- Comprehensive evaluation of productivity and (real-life) benefits and improvements

Ricerca for profit

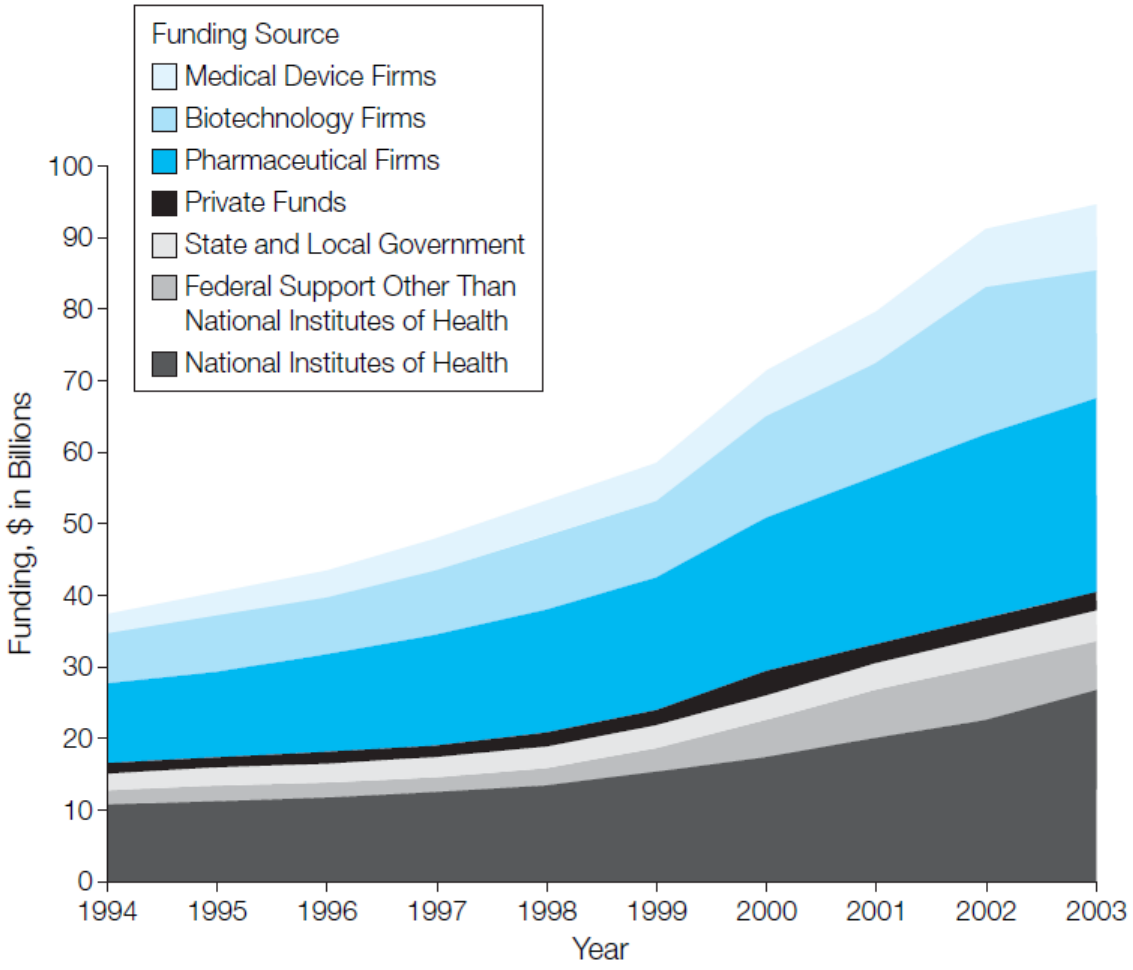
- Pipeline and selling
- Social value of research as part of the research community

- More open discussion of the research models proposed: increase multidisciplinary approaches, single-multi responsible projects and wider confrontation
- Who is responsible for overall fairness of funding?

- Better knowledge (towards society) of overall activities
- Multiple stakeholders open confrontation

US Funding for biomedical research

Figure 1. Funding for Biomedical Research by Source, 1994-2003



NIH Funding distribution: basic vs clinical/applied

Table 4. Distribution of Research Funding at the National Institutes of Health, 1994-2004

	US $ in Billions (%)										
	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004
Basic	5.9 (57)	6.1 (57)	6.4 (57)	6.9 (57)	7.4 (57)	8.6 (58)	10.1 (59)	11.6 (60)	13.0 (59)	14.1 (56)	14.8 (55)
Applied and development	4.5 (43)	4.6 (43)	4.9 (43)	5.2 (43)	5.5 (43)	6.1 (42)	6.9 (41)	7.9 (40)	9.1 (41)	11.1 (44)	12.1 (45)
Total	**10.4 (100)**	**10.7 (100)**	**11.3 (100)**	**12.1 (100)**	**12.9 (100)**	**14.7 (100)**	**17.0 (100)**	**19.5 (100)**	**22.1 (100)**	**25.2 (100)**	**26.9 (100)**

2011

32,0

Research governance funding US vs Europe

- Substantial differences in both amount of funding, research models, bottom-up vs top-down approaches, transparency of funding and capacity to respond
- In the US there is a fair balance of funding between public and private, across various drug development phases (I – IV)
- In Europe there is a lack of transparency and the proportion of public funding is much smaller and less public health oriented

- Initial degree of convergence and confrontation …
- We should ask for a more active role of truly international Agencies/bodies

Contenuti della presentazione

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RCTs and direction of effect profit vs not-for-profit

ORIGINAL CONTRIBUTION

Reported Outcomes in Major Cardiovascular Clinical Trials Funded by For-Profit and Not-for-Profit Organizations: 2000-2005

Paul M Ridker, MD

Jose Torres, BA

SURVEYS OF RANDOMIZED TRIALS published between 1990 and 2000 raised awareness in the medical community that trials funded by for-profit organizations were more likely to report positive findings than those funded by not-for-profit organizations.[1-8] As a group, these sur-

Context In surveys based on data available prior to 2000, clinical trials funded by for-profit organizations appeared more likely to report positive findings than those funded by not-for-profit organizations. Whether this situation has changed over the past 5 years or whether similar effects are present among jointly funded trials is unknown.

Objective To determine in contemporary randomized cardiovascular trials the association between funding source and the likelihood of reporting positive findings.

Design We reviewed 324 consecutive superiority trials of cardiovascular medicine published between January 1, 2000, and July 30, 2005, in *JAMA*, *The Lancet*, and the *New England Journal of Medicine*.

Main Outcome Measure The proportion of trials favoring newer treatments over the standard of care was evaluated by funding source.

JAMA 17 May 2006

RCTs and direction of effect profit vs not-for-profit

Table 2. Proportion of Trials Significantly Favoring Newer Treatments Over Standard of Care

Trials	No./Total %			*P* for Trend
	Not-for-Profit (n = 104)	Not-for-Profit and For-Profit (n = 62)	For-Profit (n = 137)	
All	51/104 (49.0)	35/62 (56.5)	92/137 (67.2)	.005
Clinical end points	19/55 (34.6)	24/44 (54.6)	64/96 (66.7)	<.001
Drug	17/43 (39.5)	24/46 (54.4)	74/113 (65.5)	.002
Device	4/8 (50.0)	9/13 (69.2)	14/17 (82.4)	.07

Conclusions Recent cardiovascular trials funded by for-profit organizations are more likely to report positive findings than trials funded by not-for-profit organizations, as are trials using surrogate rather than clinical end points. Trials jointly funded by not-for-profit and for-profit organizations appear to report positive findings at a rate approximately midway between rates observed in trials supported solely by one or the other of these entities.

JAMA. 2006;295:2270-2274 www.jama.com

Ridker PM, Torres J - JAMA 17 May 2006

Un brutto esempio di publication bias: gli antidepressivi

Selective Publication of Antidepressant Trials and Its Influence on Apparent Efficacy

Erick H. Turner, M.D., Annette M. Matthews, M.D., Eftihia Linardatos, B.S., Robert A. Tell, L.C.S.W., and Robert Rosenthal, Ph.D.

RESULTS

Among 74 FDA-registered studies, 31%, accounting for 3449 study participants, were not published. Whether and how the studies were published were associated with the study outcome. A total of 37 studies viewed by the FDA as having positive results were published; 1 study viewed as positive was not published. Studies viewed by the FDA as having negative or questionable results were, with 3 exceptions, either not published (22 studies) or published in a way that, in our opinion, conveyed a positive outcome (11 studies). According to the published literature, it appeared that 94% of the trials conducted were positive. By contrast, the FDA analysis showed that 51% were positive. Separate meta-analyses of the FDA and journal data sets showed that the increase in effect size ranged from 11 to 69% for individual drugs and was 32% overall.

NEJM, 2008

Antidepressivi e loro pubblicazione

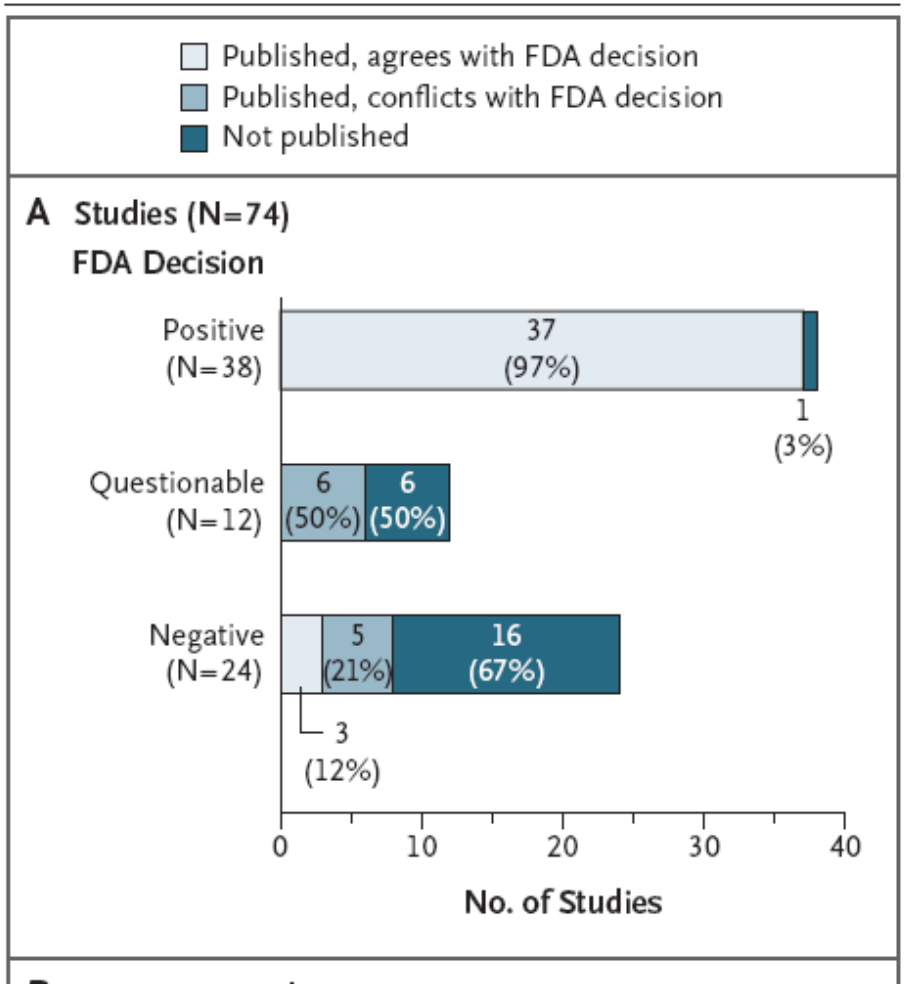


Figure 2 (facing page). Publication Status and FDA Regulatory Decision by Study and by Drug.

Panel A shows the publication status of individual studies. Nearly every study deemed positive by the FDA (top row) was published in a way that agreed with the FDA's judgment. By contrast, most studies deemed negative (bottom row) or questionable (middle row) by the FDA either were published in a way that conflicted with the FDA's judgment or were not published. Numbers shown in boxes indicate individual studies and correspond to the study numbers listed in Table A of the Supplementary Appendix. Panel B shows the numbers of patients participating in the individual studies indicated in Panel A. Data for patients who participated in studies deemed positive by the FDA were very likely to be published in a way that agreed with the FDA's judgment. By contrast, data for patients who participated in studies deemed negative or questionable by the FDA tended either not to be published or to be published in a way that conflicted with the FDA's judgment.

Un bruttissimo esempio di outcome reporting bias: gabapentina off-label

SPECIAL ARTICLE

NEJM 12 November 2009

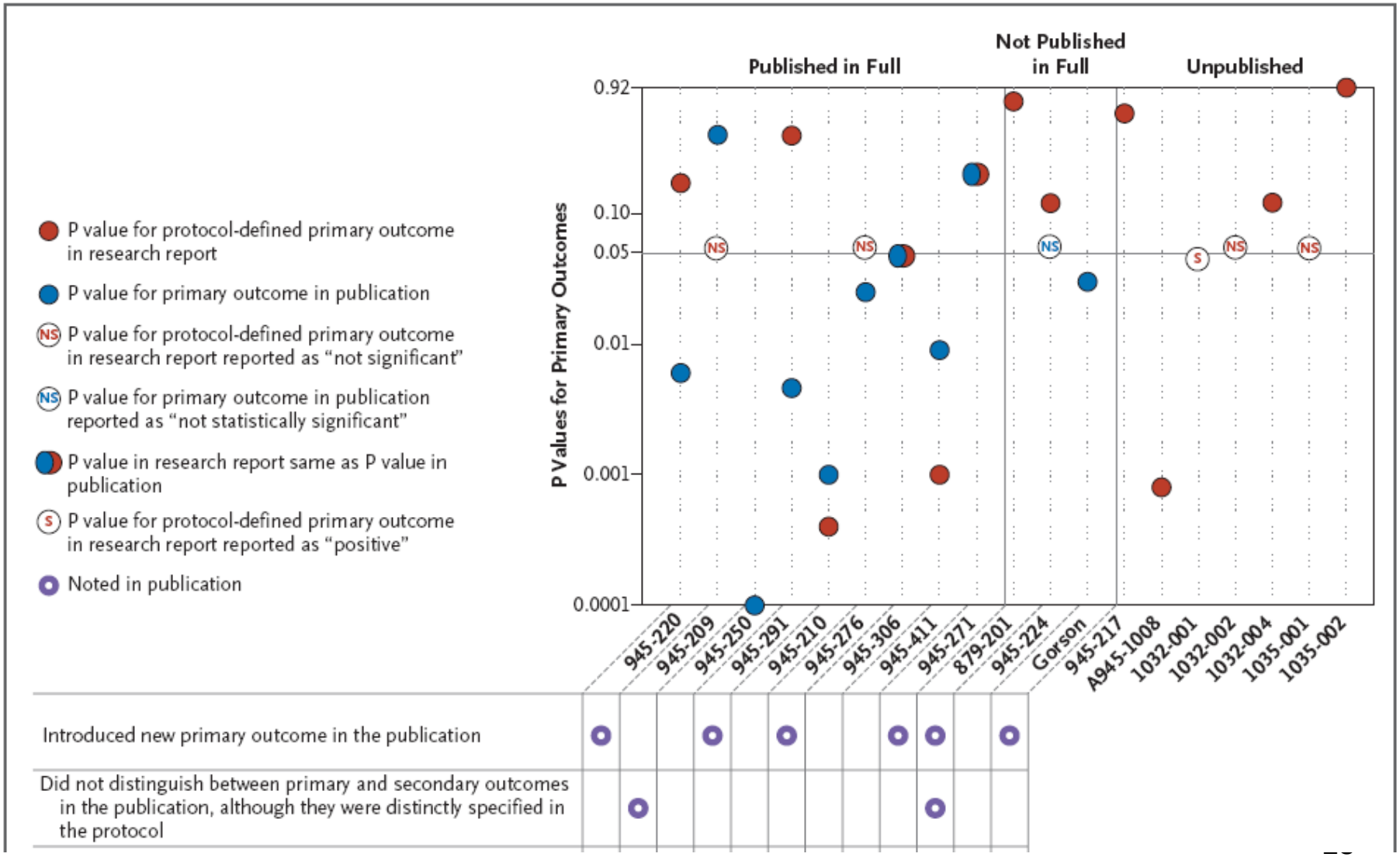
Outcome Reporting in Industry-Sponsored Trials of Gabapentin for Off-Label Use

S. Swaroop Vedula, M.D., M.P.H., Lisa Bero, Ph.D., Roberta W. Scherer, Ph.D., and Kay Dickersin, Ph.D.

RESULTS

We identified 20 clinical trials for which internal documents were available from Pfizer and Parke-Davis; of these trials, 12 were reported in publications. For 8 of the 12 reported trials, the primary outcome defined in the published report differed from that described in the protocol. Sources of disagreement included the introduction of a new primary outcome (in the case of 6 trials), failure to distinguish between primary and secondary outcomes (2 trials), relegation of primary outcomes to secondary outcomes (2 trials), and failure to report one or more protocol-defined primary outcomes (5 trials). Trials that presented findings that were not significant ($P \geq 0.05$) for the protocol-defined primary outcome in the internal documents either were not reported in full or were reported with a changed primary outcome. The primary outcome was changed in the case of 5 of 8 published trials for which statistically significant differences favoring gabapentin were reported. Of the 21 primary outcomes described in the protocols of the published trials, 6 were not reported at all and 4 were reported as secondary outcomes. Of 28 primary outcomes described in the published reports, 12 were newly introduced.

Cambiare gli outcomes degli studi



Cambiare gli outcomes degli studi significa cambiare i risultati

- Reporting biases such as those we describe here increase the likelihood that interventions will appear to be effective when they are not.
- Such biases can lead to the omission of negative findings in systematic reviews of intervention effectiveness and in evidence-based guidelines.
- For example, the 2005 Cochrane systematic review regarding the effectiveness of gabapentin for acute and chronic pain concluded that it is effective on the basis of published findings and should now be updated with the inclusion of unpublished information made available through litigation.

Vedula S, Bero L, Scherer R and Dickersin K. Outcome reporting in industry-sponsored trials of gabapentin for off-label use. NEJM 2009

RCTs in aperto vs in cieco:
sistematica
sovrastima efficacia e sottostima dei rischi

nuovi antipsicotici

Studi in aperto sugli antipsicotici nella schizofrenia:
bias in favore dei nuovi antipsicotici

THE LANCET

Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis

Stefan Leucht, Caroline Corves, Dieter Arbter, Rolf R Engel, Chunbo Li, John M Davis

Lancet 2009; 373: 31–41

Studio sponsorizzato dal NIMH

Gli studi in aperto o in singolo cieco favoriscono sistematicamente i nuovi farmaci antipsicotici

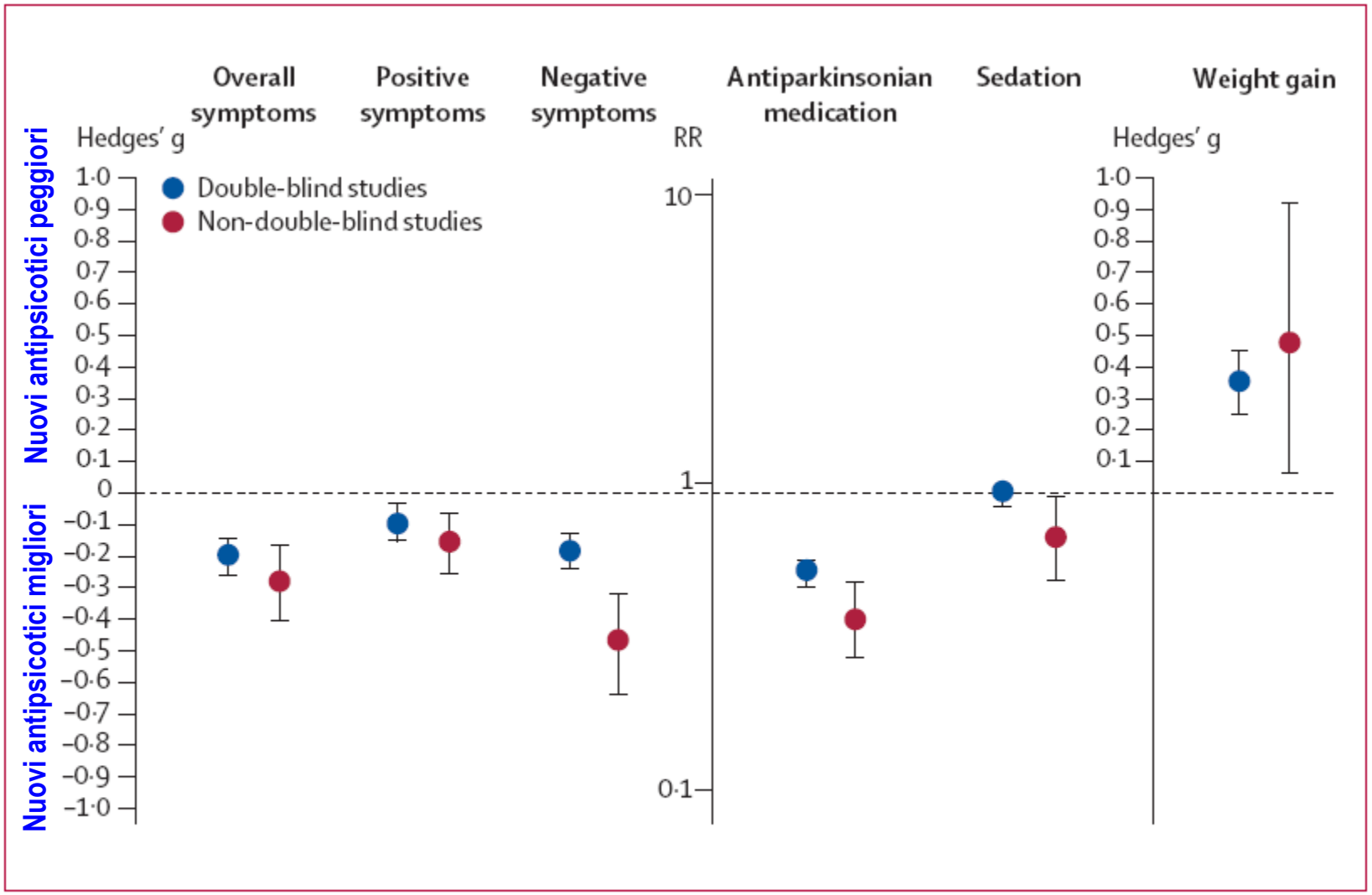


Figure 1: **Non double-blind studies favour second-generation antipsychotic drugs**
Data are Hedges' g (95% CI) and relative risk (RR; 95% CI). Similar results were obtained after correction for differences in efficacy and side-effects of the drugs. SGA=second-generation antipsychotic drug.

Antipsicotici piu o meno atipici

- *“Sembra finalmente che si debba accettare il fatto che gli antipsicotici di 2a generazione o atipici non rappresentino una reale novità terapeutica, come si era finito per credere per un decennio. Colpisce ancora di più come l’accettazione di questo giudizio si sia trasformata tanto rapidamente in un dato di fatto. Ma forse questo indica solo che ne eravamo, in fondo, consapevoli fin dall’inizio."*

Second generation antipsychotics for schizophrenia: can we resolve the conflict?
Psychol Med 2009

Milestones RCTs in the past 10 years

- Grandi RCTs pubblici (ALLHAT: hypertension, CATIE: antipsychotics, WHI estrogens increase CV events, Vitamin E increases cancer) hanno sostanzialmente ridefinito conoscenze e giudizi sui confronti nuovi e vecchi farmaci dopo oltre un decennio di studi “parziali”
- Gli studi osservazionali comparativi hanno aggiunto poco in termini di valutazioni benefici/rischi … vedi anche molto recentemente il caso rosiglitazone (Sett 2010)
- Occorre ricercare una maggiore integrazione tra conoscenze provenienti dai RCTs e tempistiche più vicine e maggiormente coordinate

Daunting *(ethical)* challenges for medical research … *to be trusted (1/2)*

- Need to manage high (often unreasonable) public expectations
- Maintain/restore public trust despite the suspicions aroused by financial conflicts of interest and research integrity
- Sustain cultural norms (independence) of academe while partnering with industry
- Obstacles to recruiting and retaining physician-scientists for translational research
- *…*

Academic medical centers and medical research
Cohen JJ and Siegel EK
JAMA. 2005;Sept 21 1367-1372.

Daunting *(ethical)* challenges for medical research … *to be trusted (2/2)*

- Widening gap between cost of research and available funding sources
- Unfunded mandates …
- Transform reward structure presently very academic (from individual scientist to teams of truly collaborating researchers/physicians)

- *Interconnectedness of these challenges magnifies difficulties and responsibilities …*

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The way ahead …
which role for RCTs and observational studies

Major step forwards: RCT Protocol registration and right to publish (data ownership)

What can be done:

- Design RCTs based on clinical end-points and medium-term duration (3-4 years) for most new drugs and perform indipendent data analysis
- Drastically reduce (avoid) non-comparative RCTs when a standard therapy exist (roflumilast, me-too biologicals, pazopanib, … quinine for cramps …)
- Plan early (multiple or multi-sites) observational (fast) comparative studies to test safety “alarming” issues in real-life population …

Evidence of comparative efficacy should have a formal role in European drug approvals

- EMA has long encouraged that, when possible, pre-market studies should be undertaken to establish comparative efficacy and risk, but has yet to set comparative assessments as the default evidentiary standard for market approval; rather, requirements for comparative studies are made on a case by case basis.
- Use of placebo is deemed unethical when there is "*a pharmacological treatment that is shown to be lifesaving or to prevent irreversible mortality*" In this case non-inferiority comparative trials are required [CPMP/ICH364/96]

Sorensen C et al BMJ 6 September 2011

Ethics Committees' advocacy role to improve the quality of RCTs

- Ask for a more stringent application of Helsinki Declaration at a regulatory level
- Support a formal role of comparative efficacy studies
- Make more evident the present anarchic framework of judging unethical studies that are regularly performed/approved for regulatory purposes

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Conclusions

- Responsibility (of enhancing research productivity and evaluation of benefit) falls on government, industry and foundations to bring these changes about with a longer-term view of research value.
- We should work to change the present suboptimal rules to bring drugs to market: risk/benefit profile should be known in terms of medium term clinical end-points in a more comparative way with indipendent access to data
- We should work to “contaminate” the values and approaches of different research communities (Cochrane and RCTs communities, guideline developers, Journals and media)

La grande intelligenza abbraccia,
la piccola intelligenza discrimina.

Lao Tse