

# Objektive Forschung der Pharmaindustrie ist möglich.

Koen Torfs

Janssen-cilag

IQWiG Herbst Symposium 27.11.2009

Help, I have to give a presentation at  
an IQWIG symposium !



# Elements of « objectivity » in research

- Pre-clinical and clinical research up to standards, regulations and good practices
  - Clinical development according to Good Clinical Practices and ethical norms
    - Appropriate research questions, fair and balanced trials designs answering relevant medical and other questions, state-of-the-art analyses
  - **Complete, fair and balanced reporting**
- 
- Tight regulation and governance in place
- Better Regulations and governance emerging

## Part I.

Fact : Significant results were<sup>(\*)</sup> more  
likely to be submitted for  
publication.  
(whatever the funding source)

(\*) hopefully « *were* »

# Factors Influencing Publication of Research Results

## Follow-up of Applications Submitted to Two Institutional Review Boards

Kay Dickersin, PhD; Yuan-I Min, MPH, MHS; Curtis L Meinert, PhD

**Objective.**—To investigate factors associated with the publication of research findings, in particular, the association between “significant” results and publication.

**Design.**—Follow-up study.

**Setting.**—Studies approved in 1980 or prior to 1980 by the two institutional review boards that serve The Johns Hopkins Health Institutions—one that serves the School of Medicine and Hospital and the other that serves the School of Hygiene and Public Health.

**Population.**—A total of 737 studies were followed up.

**Results.**—Of the studies for which analyses had been reported as having been performed at the time of interview, 81% from the School of Medicine and Hospital and 66% from the School of Hygiene and Public Health had been published. Publication was not associated with sample size, presence of a comparison group, or type of study (eg, observational study vs clinical trial). External funding and multiple data collection sites were positively associated with publication. There was evidence of publication bias in that for both institutional review boards there was an association between results reported to be significant and publication (adjusted odds ratio 2.54; 95% confidence interval, 1.63 to 3.94). Contrary to popular opinion, publication bias originates primarily with investigators, not journal editors: only six of the 124 studies not published were reported to have been rejected for publication.

**Conclusion.**—There is a statistically significant association between significant results and publication.

JAMA. 1992;267:374-378

Note :

< 10% of included studies were industry sponsored.

# Publication Bias in Editorial Decision Making

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Kay Dickersin, PhD

Annette Flanagan, RN, MA

Joseph W. Hogan, ScD

Qi Zhu, MS

Jennifer Reiling

Brian Pace, MA

**P**UBLICATION BIAS REFERS TO THE greater likelihood that studies with positive results will be published.<sup>1-3</sup> Publication bias has been demonstrated in several cohort studies that followed up protocols approved by research ethics com-

**Context** Studies with positive results are more likely to be published than studies with negative results (publication bias). One reason this occurs is that authors are less likely to submit manuscripts reporting negative results to journals. There is no evidence that publication bias occurs once manuscripts have been submitted to a medical journal.

We assessed whether submitted manuscripts that report results of controlled trials are more likely to be published if they report positive results.

**Methods** Prospective cohort study of manuscripts submitted to JAMA from February 1996 through August 1999. We classified results as positive if there was a statistically significant difference ( $P < .05$ ) reported for the primary outcome. Study characteristics and indicators for quality were also appraised. We included manuscripts that reported prospective studies in which participants were assigned to an intervention or comparison group and statistical tests compared differences between groups.

**Results** Among 745 manuscripts, 133 (17.9%) were published: 78 (20.4%) of 383 with positive results, 51 (15.0%) of 341 with negative results, and 4 (19.0%) of 21 with unclear results. The crude relative risk for publication of studies with positive results compared with negative results was 1.36 (95% confidence interval [CI], 0.99-1.88).

After being adjusted simultaneously for study characteristics and quality indicators, the odds ratio for publishing studies with positive results was 1.30 (95% CI, 0.87-1.96).

**Conclusions** Among submitted manuscripts, we did not find a statistically significant difference in publication rates between those with positive vs negative results.

Note :  
Only JAMA studies included.

## Part II.

Fact : Publications of industry sponsored studies had higher quality standards and more positive results than publications of non-industry sponsored studies

# The uncertainty principle and industry-sponsored research

*Benjamin Djulbegovic, Mensura Lacevic, Alan Cantor, Karen K Fields, Charles L Bennett, Jared R Adams, Nicole M Kuderer, Gary H Lyman*

**Background** Reporting of pharmaceutical-industry-sponsored randomised clinical trials often result in biased findings, either due to selective reporting of studies with non-equivalent arms or publication of low-quality papers, wherein unfavourable results are incompletely described. A randomised trial should be conducted only if there is substantial uncertainty about the relative value of one treatment versus another. Studies in which intervention and control are thought to be non-equivalent violates the uncertainty principle.

**Methods** We examined the quality of 136 published randomised trials that focused on one disease category (multiple myeloma) and adherence to the uncertainty principle. To evaluate whether the uncertainty principle was upheld, we compared the number of studies favouring experimental treatments over standard ones. We analysed data according to the source of funding.

**Findings** Trials funded solely or in part by 35 profit-making organisations had a trend toward higher quality scores (mean 2.94 [SD 1.3]; median 3) than randomised trials supported by 95 governmental or other non-profit organisations (2.4 [0.8]; 2;  $p=0.06$ ). Overall, the uncertainty principle was upheld, with 44% of randomised trials favouring standard treatments and 56% innovative treatments ( $p=0.17$ ); mean and median preference evaluation scores were 3.7 (1.0) and 4. However, when the analysis was done according to the source of funding, studies funded by non-profit organisations maintained equipoise favouring new therapies over standard ones (47% vs 53%;  $p=0.608$ ) to a greater extent than randomised trials supported solely or in part by profit-making organisations (74% vs 26%;  $p=0.004$ ).

**Interpretation** The reported bias in research sponsored by the pharmaceutical industry may be a consequence of violations of the uncertainty principle. Sponsors of clinical trials should be encouraged to report all results and to choose appropriate comparative controls.

*Lancet* 2000; **356**: 635–38



# Scope and Impact of Financial Conflicts of Interest in Biomedical Research

## A Systematic Review

**Context** Despite increasing awareness about the potential impact of financial conflicts of interest on biomedical research, no comprehensive synthesis of the body of evidence relating to financial conflicts of interest has been performed.

**Objective** To review original, quantitative studies on the extent, impact, and management of financial conflicts of interest in biomedical research.

**Data Sources** Studies were identified by searching MEDLINE (January 1980–October 2002), the Web of Science citation database, references of articles, letters, commentaries, editorials, and books and by contacting experts.

**Study Selection** All English-language studies containing original, quantitative data on financial relationships among industry, scientific investigators, and academic institutions were included. A total of 1664 citations were screened, 144 potentially eligible full articles were retrieved, and 37 studies met our inclusion criteria.

**Data Extraction** One investigator (J.E.B.) extracted data from each of the 37 studies. The main outcomes were the prevalence of specific types of industry relationships, the relation between industry sponsorship and study outcome or investigator behavior, and the process for disclosure, review, and management of financial conflicts of interest.

**Data Synthesis** Approximately one fourth of investigators have industry affiliations, and roughly two thirds of academic institutions hold equity in start-ups that sponsor research performed at the same institutions. Eight articles, which together evaluated 1140 original studies, assessed the relation between industry sponsorship and outcome in original research. Aggregating the results of these articles showed a statistically significant association between industry sponsorship and pro-industry conclusions (pooled Mantel-Haenszel odds ratio, 3.60; 95% confidence interval, 2.63–4.91). Industry sponsorship was also associated with restrictions on publication and data sharing. The approach to managing financial conflicts varied substantially across academic institutions and peer-reviewed journals.

**Conclusions** Financial relationships among industry, scientific investigators, and academic institutions are widespread. Conflicts of interest arising from these ties can influence biomedical research in important ways.

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*JAMA. 2003;289:454-465*

Or is industry more selective in the trials they do ?

Note :

This is a review of reviews up to 2002

# Pharmaceutical industry sponsorship and research outcome and quality: systematic review

Joel Lexchin, Lisa A Bero, Benjamin Djulbegovic, Otavio Clark

**Objective** To investigate whether funding of drug studies by the pharmaceutical industry is associated with outcomes that are favourable to the funder and whether the methods of trials funded by pharmaceutical companies differ from the methods in trials with other sources of support.

**Methods** Medline (January 1966 to December 2002) and Embase (January 1980 to December 2002) searches were supplemented with material identified in the references and in the authors' personal files. Data were independently abstracted by three of the authors and disagreements were resolved by consensus.

**Results** 30 studies were included. Research funded by drug companies was less likely to be published than research funded by other sources. Studies sponsored by pharmaceutical companies were more likely to have outcomes favouring the sponsor than were studies with other sponsors (odds ratio 4.05; 95% confidence interval 2.98 to 5.51; 18 comparisons). None of the 13 studies that analysed methods reported that studies funded by industry was of poorer quality.

**Conclusion** Systematic bias favours products which are made by the company funding the research. Explanations include the selection of an inappropriate comparator to the product being investigated and publication bias.

Or is industry more selective in the trials they do ?

BMJ VOLUME 326 31 MAY 2003 bmj.com

Note : This is a review of reviews up to 2002

Short communication

# Pharmaceutical company funding and its consequences: A qualitative systematic review<sup>☆</sup>

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## Abstract

This article systematically reviews published studies of the association of pharmaceutical industry funding and clinical trial results, as well as a few closely related studies. It reviews two earlier results, and surveys the recent literature. Results are clear: Pharmaceutical company sponsorship is strongly associated with results that favor the sponsors' interests.

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Results since 2003 support the association of industry funding with higher measures of methodological quality. With the exception of a comparison of industry and Cochrane meta-analyses [25], recent studies report that in other ways industry-funded trials are of equal or higher methodological quality than non-industry-funded trials solutions as: stronger disclosure requirements, rigorous trial reporting standards, and trial registries [5]. Because the bias is not the result of simple methodological problems, radical solutions are called for, that divorce the pharmaceutical industry from published research. In the meantime, the fact that pharmaceutical company funding has

**Note :** This is a review of reviews up 2003 to 2006

## Part III.

Fact : Industry sponsored studies were published and reported selectively

# Evidence based medicine—selective reporting from studies sponsored by pharmaceutical industry: review of studies in new drug applications

Hans Melander, Jane Ahlqvist-Rastad, Gertie Meijer, Björn Beermann

**Objectives** To investigate the relative impact on publication bias caused by multiple publication, selective publication, and selective reporting in studies sponsored by pharmaceutical companies.

**Design** 42 placebo controlled studies of five selective serotonin reuptake inhibitors submitted to the Swedish drug regulatory authority as a basis for marketing approval for treating major depression were compared with the studies actually published (between 1983 and 1999).

**Results** Multiple publication: 21 studies contributed to at least two publications each, and three studies contributed to five publications. Selective publication: studies showing significant effects of drug were published as stand alone publications more often than studies with non-significant results. Selective reporting: many publications ignored the results of intention to treat analyses and reported the more favourable per protocol analyses only.

**Conclusions** The degree of multiple publication, selective publication, and selective reporting differed between products. Thus, any attempt to recommend a specific selective serotonin reuptake inhibitor from the publicly available data only is likely to be based on biased evidence.



3 x more likely

BMJ VOLUME 326 31 MAY 2003 bmj.com

Note : SSRI studies reviewed which are submitted to authorities between 1983 and 1999



# Empirical Evidence for Selective Reporting of Outcomes in Randomized Trials

## Comparison of Protocols to Published Articles

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**S**ELECTIVE PUBLICATION OF STUDIES with statistically significant results has received widespread recognition.<sup>1</sup> In contrast, selective reporting of favorable

**Note : period covered : 1994-1995**

come reporting bias has been widely

**Note : 70% of studies included are industry funded.**

Our study had 3 goals: (1) to determine the prevalence of incomplete outcome reporting in published reports of randomized trials; (2) to assess the association between outcome reporting and statistical significance; and (3) to evaluate the consistency between primary outcomes specified in trial protocols and those defined in the published articles.

### METHODS

**Context** Selective reporting of outcomes within published studies based on the nature or direction of their results has been widely suspected, but direct evidence of such bias is currently limited to case reports.

**Objective** To study empirically the extent and nature of outcome reporting bias in a cohort of randomized trials.

**Design** Cohort study using protocols and published reports of randomized trials approved by the Scientific-Ethical Committees for Copenhagen and Frederiksberg, Denmark, in 1994-1995. The number and characteristics of reported and unreported trial outcomes were recorded from protocols, journal articles, and a survey of trialists. An outcome was considered incompletely reported if insufficient data were presented in the published articles for meta-analysis. Odds ratios relating the completeness of outcome reporting to statistical significance were calculated for each trial and then pooled to provide an overall estimate of bias. Protocols and published articles were also compared to identify discrepancies in primary outcomes.

**Main Outcome Measures** Completeness of reporting of efficacy and harm outcomes and of statistically significant vs nonsignificant outcomes; consistency between primary outcomes defined in the most recent protocols and those defined in published articles.

**Results** One hundred two trials with 122 published journal articles and 3736 outcomes were identified. Overall, 50% of efficacy and 65% of harm outcomes per trial were incompletely reported. Statistically significant outcomes had a higher odds of being fully reported compared with nonsignificant outcomes for both efficacy (pooled odds ratio, 2.4; 95% confidence interval [CI], 1.4-4.0) and harm (pooled odds ratio, 4.7; 95% CI, 1.8-12.0) data. In comparing published articles with protocols, 62% of trials had at least 1 primary outcome that was changed, introduced, or omitted. Eighty-six percent of survey responders (42/49) denied the existence of unreported outcomes despite clear evidence to the contrary.

**Conclusions** The reporting of trial outcomes is not only frequently incomplete but also biased and inconsistent with protocols. Published articles, as well as reviews that incorporate them, may therefore be unreliable and overestimate the benefits of an intervention. To ensure transparency, planned trials should be registered and protocols should be made publicly available prior to trial completion.

JAMA. 2004;291:2457-2465

# Selective Publication of Antidepressant Trials and Its Influence on Apparent Efficacy

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## BACKGROUND

Evidence-based medicine is valuable to the extent that the evidence base is complete and unbiased. Selective publication of clinical trials — and the outcomes within those trials — can lead to unrealistic estimates of drug effectiveness and alter the apparent risk–benefit ratio.

## METHODS

We obtained reviews from the Food and Drug Administration (FDA) for studies of 12 antidepressant agents involving 12,564 patients. We conducted a systematic literature search to identify matching publications. For trials that were reported in the literature, we compared the published outcomes with the FDA outcomes. We also compared the effect size derived from the published reports with the effect size derived from the entire FDA data set.

## 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.

## CONCLUSIONS

We cannot determine whether the bias observed resulted from a failure to submit manuscripts on the part of authors and sponsors, from decisions by journal editors and reviewers not to publish, or both. Selective reporting of clinical trial results may have adverse consequences for researchers, study participants, health care professionals, and patients.

N Engl J Med 2008;358:252-60.

# Publication of Clinical Trials Supporting Successful New Drug Applications: A Literature Analysis

September 2008

Kirby Lee<sup>1</sup>, Peter Bacchetti<sup>2</sup>, Ida Sim<sup>3\*</sup>

Note : Trials covered  
between 1998 and 2000

## Background

The United States (US) Food and Drug Administration (FDA) approves new drugs based on sponsor-submitted clinical trials. The publication status of these trials in the medical literature and factors associated with publication have not been evaluated. We sought to determine the proportion of trials submitted to the FDA in support of newly approved drugs that are published in biomedical journals that a typical clinician, consumer, or policy maker living in the US would reasonably search.

## Methods and Findings

We conducted a cohort study of trials supporting new drugs approved between 1998 and 2000, as described in FDA medical and statistical review documents and the FDA approved drug label. We determined publication status and time from approval to full publication in the medical literature at 2 and 5 y by searching PubMed and other databases through 01 August 2006. We then evaluated trial characteristics associated with publication. We identified 909 trials supporting 90 approved drugs in the FDA reviews, of which 43% (394/909) were published. Among the subset of trials described in the FDA-approved drug label and classified as “pivotal trials” for our analysis, 76% (257/340) were published. In multivariable logistic regression for all trials 5 y postapproval, likelihood of publication correlated with statistically significant results (odds ratio [OR] 3.03, 95% confidence interval [CI] 1.78–5.17); larger sample sizes (OR 1.33 per 2-fold increase in sample size, 95% CI 1.17–1.52); and pivotal status (OR 5.31, 95% CI 3.30–8.55). In multivariable logistic regression for only the pivotal trials 5 y postapproval, likelihood of publication correlated with statistically significant results (OR 2.96, 95% CI 1.24–7.06) and larger sample sizes (OR 1.47 per 2-fold increase in sample size, 95% CI 1.15–1.88). Statistically significant results and larger sample sizes were also predictive of publication at 2 y postapproval and in multivariable Cox proportional models for all trials and the subset of pivotal trials.

## Conclusions

Over half of all supporting trials for FDA-approved drugs remained unpublished  $\geq 5$  y after approval. Pivotal trials and trials with statistically significant results and larger sample sizes are more likely to be published. Selective reporting of trial results exists for commonly marketed drugs. Our data provide a baseline for evaluating publication bias as the new FDA Amendments Act comes into force mandating basic results reporting of clinical trials.



# Reporting Bias in Drug Trials Submitted to the Food and Drug Administration: Review of Publication and Presentation

November 2008

Kristin Rising<sup>1‡</sup>, Peter Bacchetti<sup>2</sup>, Lisa Bero<sup>3\*</sup>

## Background

Previous studies of drug trials submitted to regulatory authorities have documented selective reporting of both entire trials and favorable results. The objective of this study is to determine the publication rate of efficacy trials submitted to the Food and Drug Administration (FDA) in approved New Drug Applications (NDAs) and to compare the trial characteristics as reported by the FDA with those reported in publications.

## Methods and Findings

This is an observational study of all efficacy trials found in approved NDAs for New Molecular Entities (NMEs) from 2001 to 2002 inclusive and all published clinical trials corresponding to the trials within the NDAs. For each trial included in the NDA, we assessed its publication status, primary outcome(s) reported and their statistical significance, and conclusions. **Seventy-eight percent (128/164) of efficacy trials contained in FDA reviews of NDAs were published.** In a multivariate model, trials with favorable primary outcomes (OR = 4.7, 95% confidence interval [CI] 1.33–17.1,  $p = 0.018$ ) and active controls (OR = 3.4, 95% CI 1.02–11.2,  $p = 0.047$ ) were more likely to be published. Forty-one primary outcomes from the NDAs were omitted from the papers. Papers included 155 outcomes that were in the NDAs, 15 additional outcomes that favored the test drug, and two other neutral or unknown additional outcomes. Excluding outcomes with unknown significance, there were 43 outcomes in the NDAs that did not favor the NDA drug. Of these, 20 (47%) were not included in the papers. The statistical significance of five of the remaining 23 outcomes (22%) changed between the NDA and the paper, with four changing to favor the test drug in the paper ( $p = 0.38$ ). Excluding unknowns, 99 conclusions were provided in both NDAs and papers, nine conclusions (9%) changed from the FDA review of the NDA to the paper, and all nine did so to favor the test drug (100%, 95% CI 72%–100%,  $p = 0.0039$ ).

## Conclusions

Many trials were still not published 5 y after FDA approval. Discrepancies between the trial information reviewed by the FDA and information found in published trials tended to lead to more favorable presentations of the NDA drugs in the publications. Thus, the information that is readily available in the scientific literature to health care professionals is incomplete and potentially biased.

**Note : Trials covered in 2001 and 2002**

## Part IV.

Hypothesis : There existed publication bias in publications on publication bias. Significantly more studies are published on publication bias in industry sponsored studies than in studies sponsored by other organisations.

# Outcome reporting bias in randomized trials funded by the Canadian Institutes of Health Research

An-Wen Chan, Karmela Krleža-Jerić, Isabelle Schmid, Douglas G. Altman

**Background:** The reporting of outcomes within published randomized trials has previously been shown to be incomplete, biased and inconsistent with study protocols. We sought to determine whether outcome reporting bias would be present in a cohort of government-funded trials subjected to rigorous peer review.

**Methods:** We compared protocols for randomized trials approved for funding by the Canadian Institutes of Health Research (formerly the Medical Research Council of Canada) from 1990 to 1998 with subsequent reports of the trials identified in journal publications. Characteristics of reported and unreported outcomes were recorded from the protocols and publications. Incompletely reported outcomes were defined as those with insufficient data provided in publications for inclusion in meta-analyses. An overall odds ratio measuring the association between completeness of reporting and statistical significance was calculated stratified by trial. Finally, primary outcomes specified in trial protocols were compared with those reported in publications.

**Results:** We identified 48 trials with 68 publications and 1402 outcomes. The median number of participants per trial was 299, and 44% of the trials were published in general medical journals. A median of 31% (10th–90th percentile range 5%–67%) of outcomes measured to assess the efficacy of an intervention (efficacy outcomes) and 59% (0%–100%) of those measured to assess the harm of an intervention (harm outcomes) per trial were incompletely reported. Statistically significant efficacy outcomes had a higher odds than nonsignificant efficacy outcomes of being fully reported (odds ratio 2.7; 95% confidence interval 1.5–5.0). Primary outcomes differed between protocols and publications for 40% of the trials.

**Interpretation:** Selective reporting of outcomes frequently occurs in publications of high-quality government-funded trials.

CMAJ 2004;171(7):735-40

## Part V.

Hope : The beginning of the end of selective publishing and reporting ?

# Comparison of Registered and Published Primary Outcomes in Randomized Controlled Trials

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**Note :** 83% of the trials included here enrolled patients before July 2005 ! Since 2005, compliance with registration has improved tremendously.

tors of all clinical trials starting enrollment after July 1, 2005, to register information about the study prior to participant enrollment. Registration usually involves reporting information on the 20 items proposed by the World Health Organization registration advisory group in April 2004.<sup>2</sup> The research community has embraced this policy, as seen by

**Context** As of 2005, the International Committee of Medical Journal Editors required investigators to register their trials prior to participant enrollment as a precondition for publishing the trial's findings in member journals.

**Objective** To assess the proportion of registered trials with results recently published in journals with high impact factors; to compare the primary outcomes specified in trial registries with those reported in the published articles; and to determine whether primary outcome reporting bias favored significant outcomes.

**Data Sources and Study Selection** MEDLINE via PubMed was searched for reports of randomized controlled trials (RCTs) in 3 medical areas (cardiology, rheumatology, and gastroenterology) indexed in 2008 in the 10 general medical journals and specialty journals with the highest impact factors.

**Data Extraction** For each included article, we obtained the trial registration information using a standardized data extraction form.

**Results** Of the 323 included trials, 147 (45.5%) were adequately registered (ie, registered before the end of the trial, with the primary outcome clearly specified). Trial registration was lacking for 89 published reports (27.6%), 45 trials (13.9%) were registered after the completion of the study, 39 (12%) were registered with no or an unclear description of the primary outcome, and 3 (0.9%) were registered after the completion of the study and had an unclear description of the primary outcome. Among articles with trials adequately registered, 31% (46 of 147) showed some evidence of discrepancies between the outcomes registered and the outcomes published. The influence of these discrepancies could be assessed in only half of them and in these statistically significant results were favored in 82.6% (19 of 23).

**Conclusion** Comparison of the primary outcomes of RCTs registered with their subsequent publication indicated that selective outcome reporting is prevalent.



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

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## BACKGROUND

There is good evidence of selective outcome reporting in published reports of randomized trials.

## METHODS

We examined reporting practices for trials of gabapentin funded by Pfizer and Warner-Lambert's subsidiary, Parke-Davis (hereafter referred to as Pfizer and Parke-Davis) for off-label indications (prophylaxis against migraine and treatment of bipolar disorders, neuropathic pain, and nociceptive pain), comparing internal company documents with published reports.

## 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.

## CONCLUSIONS

We identified selective outcome reporting for trials of off-label use of gabapentin. This practice threatens the validity of evidence for the effectiveness of off-label interventions.

N Engl J Med 2009;361:1963-71.

# Topiramate in painful diabetic polyneuropathy: findings from three double-blind placebo-controlled trials

The Topiramate Diabetic Neuropathic Pain Study Group, Thienel U, Neto W, Schwabe SK, Vijapurkar U. Topiramate in painful diabetic polyneuropathy: findings from three double-blind placebo-controlled trials.

Acta Neurol Scand 2004; 110: 221–231 © Blackwell Munksgaard 2004.

**Objectives** – To evaluate the efficacy and tolerability of topiramate in patients with painful diabetic polyneuropathy. **Materials and methods** – Patients with moderate to extreme pain (0–4 Categorical Pain Scale score  $\geq 2$ ) were randomized to placebo or topiramate (100, 200, or 400 mg/day) in three similar double-blind trials. The primary efficacy analysis was pain reduction from final visit to baseline in the 100-mm Visual Analog Scale (VAS) for the intent-to-treat populations. **Results** – After 18–22 weeks of double-blind treatment, pain reductions were numerically greater with topiramate in two studies but differences between topiramate and placebo in VAS scores or in the secondary efficacy endpoints did not reach statistical significance in any of the three studies. Across all studies, 24% of topiramate-treated patients and 8% of placebo-treated patients discontinued due to adverse events; groups did not differ in the occurrence of serious adverse events.

**Conclusion** – These studies did not find topiramate to be significantly more effective than placebo in reducing pain scores in patients with painful diabetic polyneuropathy. Several design features may have precluded the studies from having sufficient sensitivity to differentiate effective and ineffective treatments. The study design and results are instructive for other investigators designing future clinical studies in neuropathic pain.

**The Topiramate Diabetic Neuropathic Pain Study Group\*, U. Thienel<sup>1</sup>, W. Neto<sup>2</sup>, S. K. Schwabe<sup>2</sup>, U. Vijapurkar<sup>2</sup>**

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\*Investigator listing can be found as an Appendix in the online version of this article.

Key words: topiramate; diabetic neuropathy; neuropathic pain

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# Topiramate monotherapy in the management of acute mania: results of four double-blind placebo-controlled trials

Kushner SF, Khan A, Lane R, Olson WH. Topiramate monotherapy in the management of acute mania: results of four double-blind placebo-controlled trials.

Bipolar Disord 2006; 8: 15–27. © Blackwell Munksgaard, 2006

**Objective:** To evaluate the efficacy and tolerability of topiramate monotherapy in adults with acute manic or mixed episodes of bipolar I disorder.

**Methods:** In four trials, adults hospitalized with acute mania, a diagnosis of bipolar I disorder, history of  $\geq 1$  previous manic or mixed episodes, and  $\geq 20$  Young Mania Rating Scale (YMRS) score were randomized to double-blind treatment with topiramate (target doses: 200, 400, or 600 mg/day) or placebo; two trials included an active comparator (lithium, 1500 mg/day). The core study duration in all trials was 3 weeks; three trials also had 9-week double-blind extensions. The primary efficacy variable was mean change from baseline in YMRS in the core 3-week study.

**Results:** Changes in YMRS score during 3 weeks were not significantly different for topiramate versus placebo (mean YMRS reductions,  $-5.1$  to  $-8.4$ ). Mean YMRS reductions in lithium-treated groups were significantly greater ( $p \leq 0.001$  versus placebo and topiramate). A similar pattern was observed after 12 weeks of double-blind treatment in studies with double-blind extensions. Paresthesia, appetite decrease, dry mouth, and weight loss were more frequently associated with topiramate than with placebo.

**Conclusions:** These studies do not support the efficacy of topiramate as monotherapy in acute mania or mixed episodes in adults with bipolar I disorder. Topiramate was not associated with mood destabilization measured as mania exacerbation or treatment-emergent depression. Lithium was confirmed as an effective therapy in this population.

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Key words: acute mania – bipolar I disorder – lithium – topiramate – weight loss

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# Effectiveness of antipsychotic drugs in first-episode schizophrenia and schizophreniform disorder: an open randomised clinical trial

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## Summary

**Background** Second-generation antipsychotic drugs were introduced over a decade ago for the treatment of schizophrenia; however, their purported clinical effectiveness compared with first-generation antipsychotic drugs is still debated. We aimed to compare the effectiveness of second-generation antipsychotic drugs with that of a low dose of haloperidol, in first-episode schizophrenia.

**Methods** We did an open randomised controlled trial of haloperidol versus second-generation antipsychotic drugs in 50 sites, in 14 countries. Eligible patients were aged 18–40 years, and met diagnostic criteria for schizophrenia, schizophreniform disorder, or schizoaffective disorder. 498 patients were randomly assigned by a web-based online system to haloperidol (1–4 mg per day; n=103), amisulpride (200–800 mg per day; n=104), olanzapine (5–20 mg per day; n=105), quetiapine (200–750 mg per day; n=104), or ziprasidone (40–160 mg per day; n=82); follow-up was at 1 year. The primary outcome measure was all-cause treatment discontinuation. Patients and their treating physicians were not blinded to the assigned treatment. Analysis was by intention to treat. This study is registered as an International Standard Randomised Controlled Trial, number ISRCTN68736636.

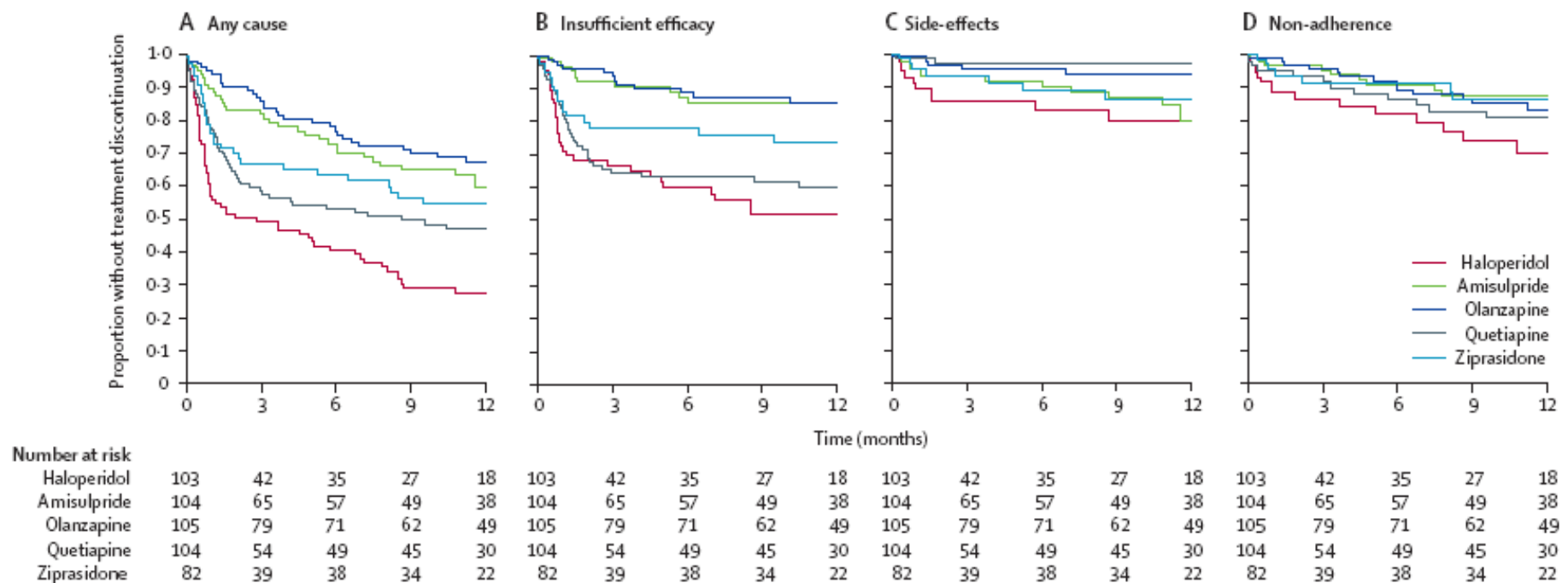
**Findings** The number of patients who discontinued treatment for any cause within 12 months was 63 (Kaplan-Meier estimate 72%) for haloperidol, 32 (40%) for amisulpride, 30 (33%) for olanzapine, 51 (53%) for quetiapine, and 31 (45%) for ziprasidone. Comparisons with haloperidol showed lower risks for any-cause discontinuation with amisulpride (hazard ratio [HR] 0·37, [95% CI 0·24–0·57]), olanzapine (HR 0·28 [0·18–0·43]), quetiapine (HR 0·52 [0·35–0·76]), and ziprasidone (HR 0·51 [0·32–0·81]). However, symptom reductions were virtually the same in all the groups, at around 60%.

**Interpretation** This pragmatic trial suggests that clinically meaningful antipsychotic treatment of first-episode of schizophrenia is achievable, for at least 1 year. However, we cannot conclude that second-generation drugs are more efficacious than is haloperidol, since discontinuation rates are not necessarily consistent with symptomatic improvement.

**Funding** AstraZeneca, Pfizer, Sanofi-Aventis.

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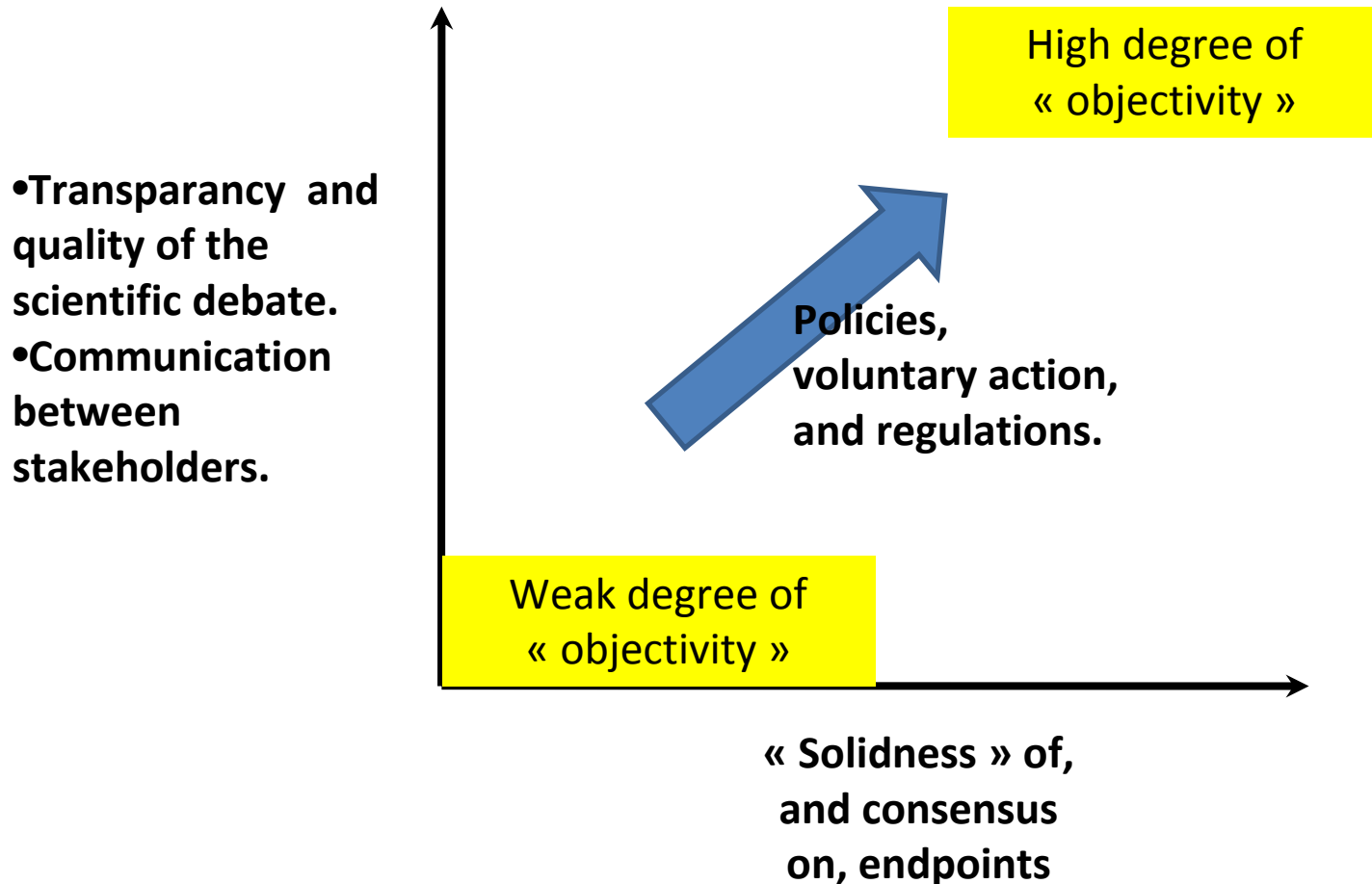
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Example of independent non-governmental body, increasing the transparency and quality of the scientific debate in oncology.

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Everyone must be considered as an individual.

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Compensation must be fair and adequate,  
and working conditions clean, orderly and safe.

We must be mindful of ways to help our employees fulfill  
their family responsibilities.

Employees must feel free to make suggestions and complaints.  
There must be equal opportunity for employment, development  
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We must provide competent management,  
and their actions must be just and ethical.

We are responsible to the communities in which we live and work  
and to the world community as well.

We must be good citizens — support good works and charities  
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We must maintain in good order  
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Research must be carried on, innovative programs developed  
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New equipment must be purchased, new facilities provided  
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Reserves must be created to provide for adverse times.

When we operate according to these principles,  
the stockholders should realize a fair return.

*Johnson & Johnson*

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  - MOOSE for meta-analysis of observational studies
  - QUORUM (PRISMA) for systematic reviews and meta-analyses of randomised trials
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  - Council of Science Editors White Paper on « Promoting Integrity in Scientific Journal Publications ».

