



Pooled-Trials Publication Bias

Are negative antidepressant trials hidden from view?

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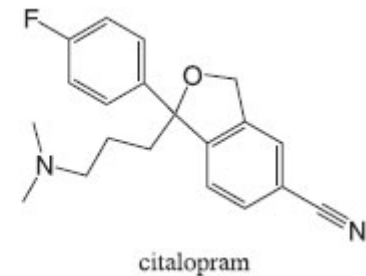
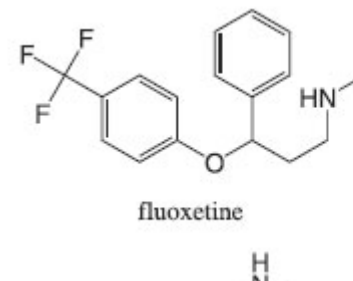


Disclosures

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Depression

- > Depression
 - Lifetime prevalence: 20%¹
 - In top 5 diseases with highest disease burden²
- > Second-generation antidepressants
 - SSRIs, SNRIs



¹NEMESIS-2 2010²Murray et al. Lancet 2012



- **Study publication bias:** Positive studies are more likely to be published



File drawer effect

Higgins and Green Cochrane Collaboration 2011



The NEW ENGLAND JOURNAL of MEDICINE

SPECIAL ARTICLE

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.



Method

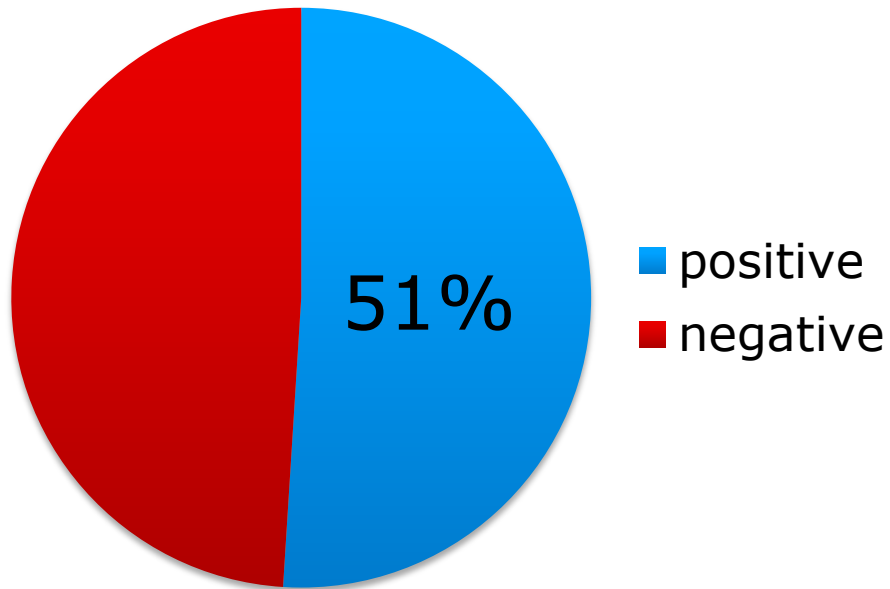
- > Food and Drug Administration (FDA) reviews
 - <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>

The screenshot shows the Drugs@FDA website interface. At the top, there is a navigation bar with tabs for Home, Food, Drugs, Medical Devices, Vaccines, Blood & Biologics, Animal & Veterinary, Cosmetics, Radiation-Emitting Products, and Tobacco Products. Below the navigation bar, there is a breadcrumb trail: FDA Home > Drug Databases > Drugs@FDA. On the right side, there are icons for printing, a red cross, and an envelope. The main content area features the Drugs@FDA logo and the text "FDA Approved Drug Products". To the right of the logo, there are links for "FAQ | Instructions | Glossary | Contact Us" and "Drugs@FDA Demo | What's New in Drugs@FDA". Below the logo, there is a search bar with the text "Search by Drug Name, Active Ingredient, or Application Number". The search bar contains the text "Enter at least three characters:" followed by an input field, a "Submit" button, a "Clear" button, and a link for "Advanced Search". At the bottom left, there is a link for "Browse by Drug Name".

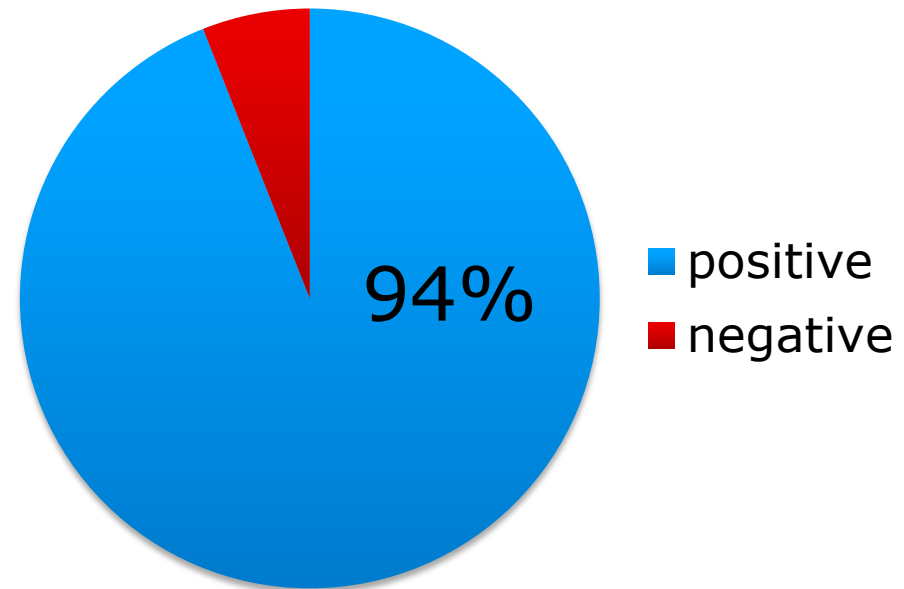


Depression

FDA



Literature



Turner et al. 2008 NEJM



INDIANAPOLIS, Jan 18, 2008 /PRNewswire-FirstCall via COMTEX News Network/ -- Eli Lilly and Company strongly objects to implications in a New York Times article published Thursday that the company has suppressed results of negative clinical trials.

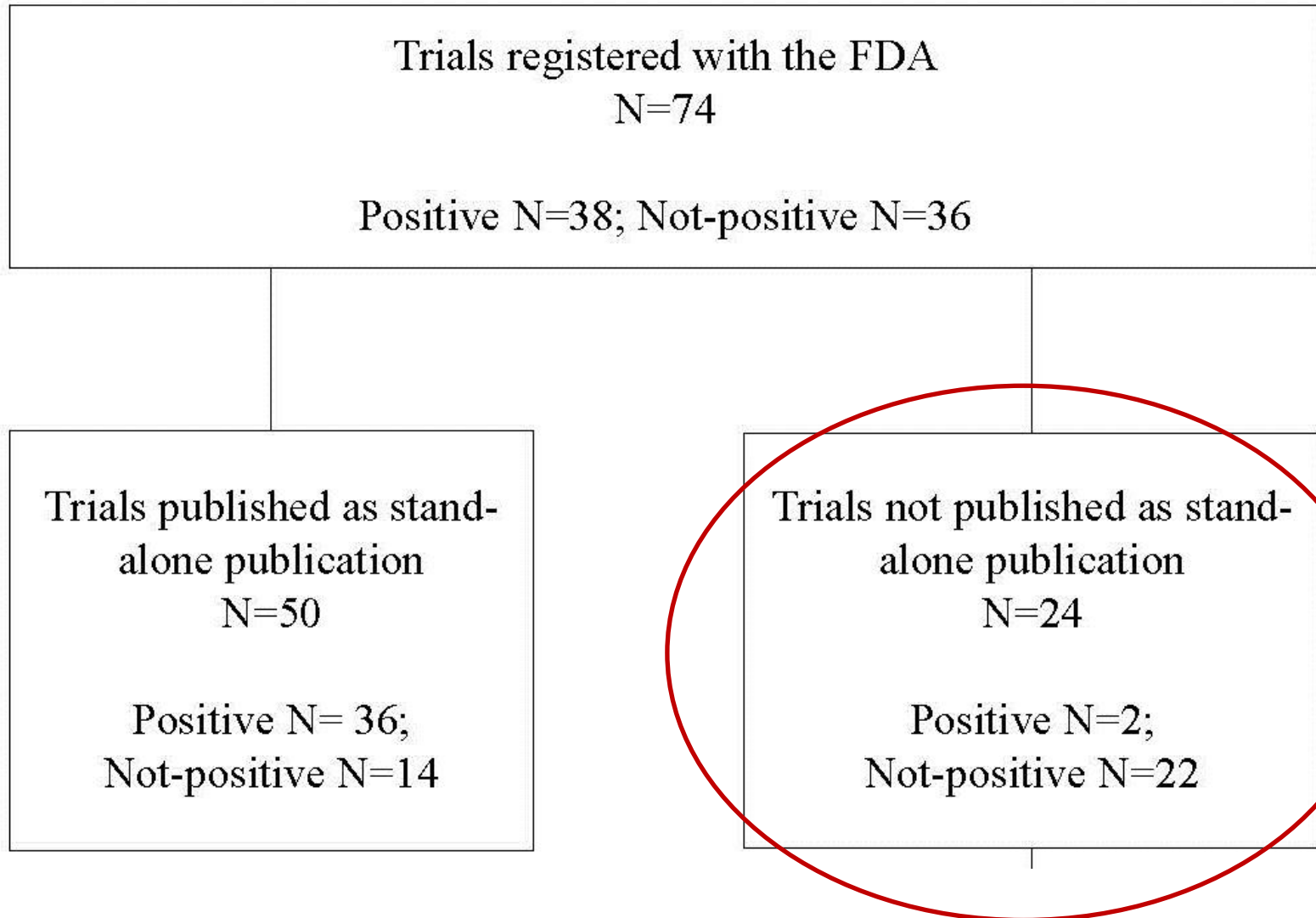
In addition, the two Cymbalta studies listed in an appendix to the NEJM article as "unpublished" have, in fact, been published in peer-reviewed journals. The results of HMAT-A and HMAQ-B were published twice -- first in the Autumn 2002 issue of Psychopharmacology Bulletin, and again in the Primary Care Companion Journal of Clinical Psychiatry in

The authors of the NEJM article decided not to count studies as "published" if the manuscript included data from two or more studies. While this methodology might be suitable for an academic discussion, it's clearly not the appropriate standard for determining whether a company has been transparent in disclosing its data.



Research questions

1. Are “unpublished” negative antidepressant trials published (exclusively) in pooled-trials publications?
2. Do these publications answer the primary research question?
3. How often do pooled-trials publications reach positive conclusions?





Trials not published as stand-
alone publication
N=24

Positive N=2;
Not-positive N=22

Trials published in pooled-trials
publications
N=20

Positive N= 2;
Not-positive N=18

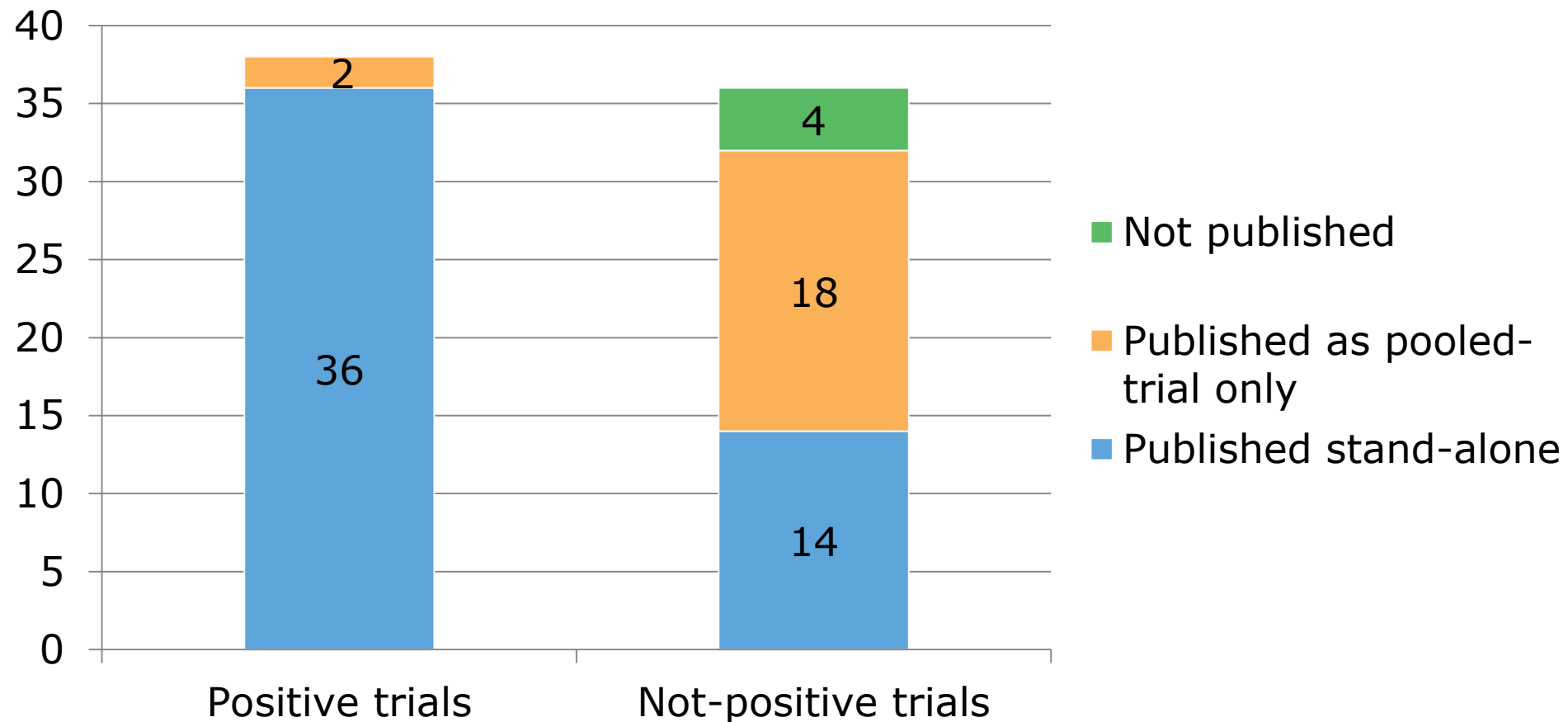
Trials not published
N=4

Positive N=0;
Not-positive N=4

86 pooled-trials publications



Negative trials published in pooled-trials publications





1. Are `unpublished` negative antidepressant trials published (exclusively) in pooled-trials publications?

- RR: 9.50; 95% CI: 2.37-38.06; $p < 0.001$.



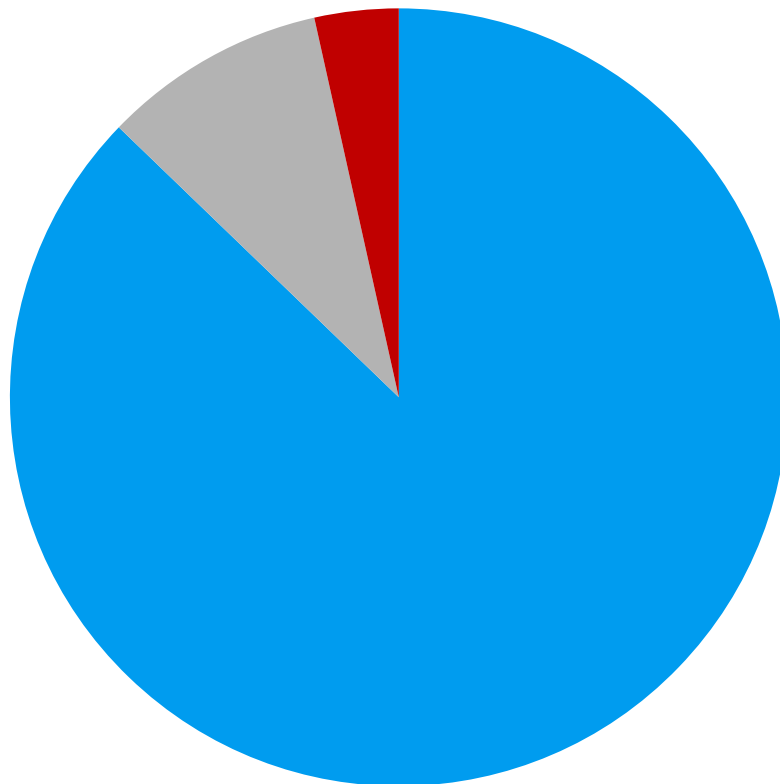
2. Do these publications answer the primary research question?

- > Primary research question was answered for only 7 (35%) of 20 trials
- > Only 3 publications (3%) reporting on 3 trials presented individual efficacy data
 - Not reported for 17 trials (2 positive)
- > Pooled-trials publications reported on:
 - Secondary outcomes
 - Subgroups
 - Safety



3. How often do pooled-trials publications reach positive conclusions?

86 publications



- Positive (87%)
- Neutral (9%)
- Negative (3%)



Conclusion

- > Negative trials published in pooled-trials publications, that:
 - Do not present results individual trials,
 - Focus on secondary endpoints,
 - Have positive conclusions.



Take home messages:

- > Pooled-trials publications flood the evidence base with positive articles
- > Pooled-trials publication bias inflates the apparent efficacy of antidepressants



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MSc



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Duloxetine (2 negative trials)

- > Individual trial results were presented, however:
 - Trial 1 → 31 publications
 - Trial 2 → 38 publications

- > “Salami slicing” of duloxetine trials¹
 - Subgroups
 - Safety

¹Spielmans et al., *Psychother Psychosom*, 2010



Implications

- > Marketing tool
- > More subtle types of bias become more important



Solutions

- > Pooled-trials publications should not be included in meta-analyses

- > Contribution to literature or not?

- > Pooled-trials publications should include:
 - Individual trial results
 - References to primary efficacy results