Selective Publication of Antidepressant Trials and Its Influence on Apparent Efficacy

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FROM ABSTRACT

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 3,449 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 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.
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.

THESE AUTHORS ALSO NOTE:

“Medical decisions are based on an understanding of publicly reported clinical trials. If the evidence base is biased, then decisions based on this evidence may not be the optimal decisions. 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.” [Very Important]

“How accurately does the published literature convey data on drug efficacy to the medical community? To address this question, we compared drug efficacy inferred from the published literature with drug efficacy according to FDA reviews.”

These authors looked at the data from clinical-trials for 12 antidepressant drugs approved by the FDA between 1987 and 2004, involving 12,564 adult patients. For 8 of the 12 drugs, the authors obtained hard copies of statistical and medical reviews through the Freedom of Information Act.

RESULTS

“Of the 74 FDA-registered studies in the analysis we could not find evidence of publication for 23 (31%).”

“The FDA deemed 38 of the 74 studies (51%) positive, and all but 1 of the 38 were published.”

“The remaining 36 studies (49%) were deemed to be either negative (24 studies) or questionable. Of these 36 studies, 3 were published as not positive, whereas the remaining 33 either were not published (22 studies) or were published, in our opinion, as positive and therefore conflicted with the FDA’s conclusion.” [Wow]

“Overall, the studies that the FDA judged as positive were approximately 12 times as likely to be published in a way that agreed with the FDA analysis as were studies with nonpositive results according to the FDA.”

“According to the FDA, 38 of the 74 registered studies had positive results (51%).”
DISCUSSION

“We found a bias toward the publication of positive [antidepressant drug] results.”

“Not only were positive results more likely to be published, but studies that were not positive, in our opinion, were often published in a way that conveyed a positive outcome.”

These authors found that the efficacy of antidepressant drugs is “less than would be gleaned from an examination of the published literature alone. According to the published literature, the results of nearly all of the trials of antidepressants were positive. In contrast, FDA analysis of the trial data showed that roughly half of the trials had positive results. The statistical significance of a study’s results was strongly associated with whether and how they were reported.” [Important]

“Among the 74 studies reviewed by the FDA, 38 were deemed to have positive results, 37 of which were published with positive results; the remaining study was not published.”

“Among the studies deemed to have questionable or negative results by the FDA, there was a tendency toward nonpublication or publication with positive results, conflicting with the conclusion of the FDA.”

“Among the 12,564 patients in all 74 studies, 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. In contrast, data for patients participating in studies deemed questionable or negative by the FDA tended either not to be published or to be published in a way that conflicted with the FDA’s judgment.”

The 12 antidepressant drugs reviewed in this study were:

Bupropion SR (Wellbutrin SR, GlaxoSmithKline)
Citalopram (Celexa, Forest)
Duloxetine (Cymbalta, Eli Lilly)
Escitalopram (Lexapro, Forest)
Fluoxetine (Prozac, Eli Lilly)
Mirtazapine (Remeron, Organon)
Nefazodone (Serzone, Bristol-Myers Squibb)
Paroxetine (Paxil, GlaxoSmithKline)
Paroxetine CR (Paxil CR, GlaxoSmithKline)
Sertraline (Zoloft, Pfizer)
Venlafaxine (Effexor, Wyeth)
Venlafaxine XR (Effexor XR, Wyeth)
These authors cite references that the selective publication of safety issues that may distort the risk–benefit ratio has been a problem with Vioxx, and with the use of selective serotonin-reuptake inhibitors for depression in children.

This study indicates that the “true magnitude of each drug’s superiority to placebo was less than a diligent literature review would indicate.” [Important]

Selective reporting of drug benefits, as noted in this study, deprives researchers of the accurate data they need, waste resources and the contributions of investigators and study participants, and they hinder the advancement of medical knowledge.

“By altering the apparent risk–benefit ratio of drugs, selective publication can lead doctors to make inappropriate prescribing decisions that may not be in the best interest of their patients and, thus, the public health.” [Very Important]

KEY POINTS FROM DAN MURPHY

<table>
<thead>
<tr>
<th>Drug</th>
<th>No. of studies</th>
<th>No. of unpublished negative studies</th>
<th>No. of published studies that conflict with the FDA</th>
<th>No. of positive published studies</th>
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<td>3</td>
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<tr>
<td>Paxil</td>
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<td>6</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>Zoloft</td>
<td>5</td>
<td>3</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

1) “Evidence-based medicine is valuable to the extent that the evidence base is complete and unbiased.” This article documents significant “selective publication” of clinical trials and the outcomes of those trials, including claiming the results are positive when in fact the data show a negative result. This “selective publication” can be the result of the authors, the sponsors, or from decisions by journal editors.

2) This study found that 31% of FDA-registered studies on antidepressant drugs, were not published, and they were not published because they were associated with a negative outcome.

3) Antidepressant drug studies viewed by the FDA as having negative or questionable results were either not published (22 studies) or published in a way that, in our opinion, conveyed a positive outcome (11 studies).
4) According to the published literature on antidepressant drugs, it appeared that 94% of the trials conducted were positive. By contrast, the FDA analysis showed that 51% only were positive.

5) Selective reporting of clinical trial results may have adverse consequences for researchers, study participants, health care professionals, and patients.

6) “Medical decisions are based on an understanding of publicly reported clinical trials. If the evidence base is biased, then decisions based on this evidence may not be the optimal decisions. 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.” [*Very Important*]

7) It can be difficult to obtain unpublished negative drug studies that are filed with the FDA. For 8 of the 12 drugs, the authors obtained hard copies of statistical and medical reviews through the Freedom of Information Act.

8) In this study, according to the FDA, 51% of antidepressant drug studies show positive results, and they are nearly all published. However, 49% of antidepressant drug studies show either negative results and are therefore not published, or they were published but spun to be a positive result, even though such studies conflicted with the FDA’s conclusion.

9) There is a bias toward the publication of positive antidepressant drug results.

10) “Not only were positive results more likely to be published, but studies that were not positive, in our opinion, were often published in a way that conveyed a positive outcome.” [*Amazing*]

11) These authors found that the efficacy of antidepressant drugs is “less than would be gleaned from an examination of the published literature alone. According to the published literature, the results of nearly all of the trials of antidepressants were positive. In contrast, FDA analysis of the trial data showed that roughly half of the trials had positive results. The statistical significance of a study’s results was strongly associated with whether and how they were reported.” [*Important*]

12) “Among the studies deemed to have questionable or negative results by the FDA, there was a tendency toward nonpublication or publication with positive results, conflicting with the conclusion of the FDA.”

13) There is evidence of “selective publication” of safety issues that distort the risk–benefit ratio with Vioxx and with the use of selective serotonin-reuptake inhibitors for depression in children.

14) This study indicates that the “true magnitude of each drug’s superiority to placebo was less than a diligent literature review would indicate.” [*Important*]
15) Selective reporting of drug benefits, as noted in this study, deprives researchers of the accurate data they need, waste resources and the contributions of investigators and study participants, and they hinder the advancement of medical knowledge.

16) “By altering the apparent risk–benefit ratio of drugs, selective publication can lead doctors to make inappropriate prescribing decisions that may not be in the best interest of their patients and, thus, the public health.” [Very Important]

COMMENTS FROM DAN MURPHY

These authors show that there is a problem in evidence-based medicine because of selective reporting in the published literature.

Every antidepressant drug reviewed in this study had at least one negative unpublished study or a published study with a conclusion that conflicted with the FDA. My review of the charts provided indicate the following:

Zoloft did poorly. Out of 5 published studies on Zoloft, 3 were negative and unpublished, and 1 was published but conflicted with the FDA. Only 1 was positive, and of course published.

Paxil also did poorly. Out of 16 published studies on Paxil, 5 were negative and unpublished, and 1 was published but conflicted with the FDA. 7 were positive, and of course all published.

For Celexa, out of 5 published studies, 1 was negative and unpublished, and 2 were published but conflicted with the FDA. 2 studies were positive and both were published.

For Wellbutrin, out of 3 published studies, 2 were negative and unpublished, and 1 was positive and published.