

The Impact of Selective Publication on Antidepressant Drug Clinical Trials

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A recent *New England Journal of Medicine* article¹ argues that selective publication of antidepressant trials may be a larger issue than many health care practitioners realize. Selective publication occurs when clinical trials with positive or favorable results are published with greater speed and frequency than trials with negative or unfavorable results. Positive results are more newsworthy and may receive publication preference from publishers; sponsoring manufacturers may suppress publication of unfavorable data; or investigators may not pursue publication of what might be perceived as inferior data. While the theoretical impact of selective publication is accepted, limited information is available to quantify the impact of the reality.

Turner et al identified all phase 2 and 3 clinical trials programs for antidepressants approved by the FDA between 1987 and 2004. The specific agents included in the study are shown in Table 1 and organized by pharmacological class. The investigators ensured that all published trials were located by conducting an extensive literature search and contacting manufacturers.

Seventy-four studies were registered with the FDA. Of these, the FDA determined 38 (51%) were determined to have a positive

outcome and all but one were published. Of the 36 remaining unpublished, the FDA stated that the results of 24 were negative and results of 12 were questionable. The calculated risk ratio for publication of a study with positive results was 11.7 (95% CI 6.2 to 22, $p < 0.001$) meaning that a study with positive results was about 12 times more likely to be published than a study with negative or questionable results. A concerning issue in 11 trials is that the primary endpoint reported to the FDA in the pre-specified methods was reported differently in the published article. Further, the authors found that positive secondary outcomes were highlighted as primary outcomes.¹

Table 1. Antidepressants Approved by the FDA, 1987-2004

<i>Selective Serotonin Reuptake Inhibitors</i>		
Citalopram	Celexa®	Forest
Escitalopram	Lexapro®	Forest
Fluoxetine	Prozac®	Eli Lilly
Paroxetine	Paxil®	GlaxoSmithKline
Paroxetine CR	Paxil CR®	GlaxoSmithKline
Sertraline	Zoloft®	Pfizer
<i>Atypical Antidepressants</i>		
Bupropion	Wellbutrin XL®	GlaxoSmithKline
Duloxetine	Cymbalta®	Eli Lilly
Mirtazapine	Remeron®	Organon
Nefazodone	Serzone®	Bristol-Myers Squibb
Venlafaxine	Effexor®	Wyeth
Venlafaxine XR	Effexor XR®	Wyeth

A statistically significant difference in effect size was found. The authors calculated that the effect size from published data is three times greater than the effect size when the FDA program data were included. The authors' concern is valid that "inflated effect sizes" can "lead to underestimates of the sample size required to achieve statistical

significance" and, therefore, waste resources underpowered studies.¹

References

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Pharmacogenetics: Potential Basis for Variable Patient Response to Selective Serotonin Reuptake Inhibitors (SSRIs)

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Selective serotonin reuptake inhibitors (SSRIs) were introduced in the 1980s and offer improved tolerability compared to older antidepressant agents such as monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants (TCAs). Despite these advantages, not all patients benefit from treatment. A significant percentage of patients do not respond adequately, while others experience adverse reactions.

An intriguing cause of variable response is the influence of genetic mechanisms, a relatively new area of study called pharmacogenetics. Accounting for differences in an individual's genetic makeup is key to creating personalized drugs with greater antidepressant efficacy and safety. Identifying differences between populations with little or no clinical response to SSRIs and those affected by uncommon side effects has tremendous potential clinical utility for depression pharmacotherapy.

Emerging scientific evidence suggests that gene variants within the serotonin transporter^{1,2} and CYP450 drug-metabolizing enzymes³ may have particular importance in the success of SSRI antidepressant therapy. A recent National Institute of Mental Health (NIMH)

study^{4,5} linked specific variations in two genes to incidence of suicidal thinking that sometimes accompanies the use of citalopram (Celexa®). Both genetic markers are represented by genes that encode for ionotropic glutamate receptors, components of the brain's glutamate neurotransmitter system, which have been associated with antidepressant response.

Hopefully, genetic testing and expansion of pharmacogenomics will help identify the parameters making it possible to predict therapeutic responses to antidepressant agents, and thus lead to individualized treatment for depression. Knowledge of genetic variation that impacts antidepressant efficacy, drug biotransformation and appearance of uncommon but serious side effects, such as suicidal behavior, ultimately has implications for the clinical management of depression with SSRIs.

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