

Antidepressants Proven to Work Only Slightly Better Than Placebo

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Although antidepressant medication is widely regarded as effective, a recent meta-analysis of published clinical trials indicates that **75 percent of the response to antidepressants is duplicated by placebo.**

The report analyses the data submitted to the U.S. Food and Drug Administration (FDA) for approval of recent antidepressant medications.

We analyzed the efficacy data submitted to the FDA for the six most widely prescribed antidepressants approved between 1987 and 1999:

- Prozac
- Paxi
- Zoloft
- Effexor
- Serzone and
- Celexa.

Results are reported from all well controlled efficacy trials of the use of these medications for the treatment of depression. FDA medical and statistical reviewers had access to the raw data and evaluated the trials independently. The findings of the primary medical and statistical reviewers were verified by at least one other reviewer, and the analysis was also assessed by an independent advisory panel.

More important, the FDA data constitute the basis on which these medications were approved. Approval of these medications implies that these particular data are strong enough and reliable enough to warrant approval. To the extent that these data are flawed, the medications should not have been approved.

In order to generalize the findings of the clinical trial to a larger patient population, **FDA reviewers sought a completion rate of 70% or better for these typically 6-week trials. Only 4 of 45 trials, however, reached this objective.**

In clinical trials, the effect of the active drug is assumed to be the difference between the drug response and the placebo response.

This report showed that the FDA clinical trials data indicate that 18% of the drug response is due to the pharmacological effects of the medication. Overall, the drug/placebo difference was less than 2 points on the HAM-D, a highly reliable physician-rated scale that has been reported to be more sensitive than patient-rated scales to drug/placebo differences.

Although mean differences were small, most of them favored the active drug, and overall, the difference was statistically significant. There were only 4 trials in which mean improvement scores in the placebo condition were equal to or higher than those in the drug condition, and in no case was placebo significantly more effective than active drug. This may indicate a small but significant drug effect. However, it is also possible that this difference between drug and placebo is an enhanced placebo effect due to the breaking of blind.

These data raise questions about the criteria used by the FDA in approving antidepressant medications. The FDA required positive findings from at least two controlled clinical trials, but the total number of trials can vary. Positive findings consist of statistically significant drug/placebo differences. The clinical significance of these differences is not considered.

To summarize, the data submitted to the FDA reveal a small but significant difference between antidepressant drug and inert placebo. This difference may be a true pharmacological effect, or it may be an artifact associated with the breaking of blind by clinical trial patients and the psychiatrists who are rating the severity of their conditions.

In any case, the difference is relatively small (about 2 points on the HAM-D), and its clinical significance is dubious. Research is therefore needed to assess the additivity of antidepressant drug and placebo effects. If there is a powerful antidepressant effect, then it is being masked by a nonadditive placebo effect, in which case current clinical trial methodology may be inappropriate for evaluating these medications, and alternate methodology need to be developed.

Conversely, if the drug effect is as small as it appears when drug/placebo differences are estimated, then there may be little justification for the clinical use of these medications.

The problem, then, would be to find an alternative, as the clinical response to both drug and placebo is substantial. Placebo treatment has the advantage of eliciting fewer side effects. However, the deception that is inherent in clinical administration of placebos inhibits their use. Thus, the development of nondeceptive methods of eliciting the placebo effect would be of great importance.

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