

Review: lower doses of antidepressant drugs are effective and have fewer adverse effects in depression

Bollini P, Pampallona S, Tibaldi G, et al. *Effectiveness of antidepressants. Meta-analysis of dose-effect relationships in randomised clinical trials. Br J Psychiatry* 1999 Apr;174:297-303.

Questions

In patients with depression, are high doses of antidepressants more effective than low doses, and how is safety affected?

Data sources

Studies were identified by searching Medline, Current Contents, and the Cochrane Collaboration Register of Trials; scanning the bibliographies of retrieved articles; and contacting authors.

Study selection

Randomised controlled trials were selected if they compared 2 different doses of the same antidepressant drug in patients with depression (>5 patients per treatment group) who were followed for at least 3 weeks.

Data extraction

Data were extracted on patient characteristics, treatment type, number of patients clinically improved (defined as a reduction of >50% of the total score on the Hamilton Rating Scale for Depression, moderate to marked improvement on the Clinical Global Impression Scale, or lack of relapse of depressive episode), and total number of side effects. All antidepressants given were converted to the equivalent doses of imipramine.

Main results

33 studies met the selection criteria. By using an intention-to-treat analysis and the dose level of 100 to 200 mg of imipramine equivalents, a mean clinical improvement of 53% was shown, which was statistically different from placebo (table). Higher or lower doses did not show improved effectiveness (table). Adverse events increased with dose, but the differences between doses were not statistically significant (table).

Conclusion

Doses of antidepressant drugs below and above the therapeutic range of 100–200 mg of imipramine equivalents do not lead to lower or higher rates of clinical improvement, whereas adverse effects increase with higher doses.

COMMENTARY

The review by Bollini and colleagues shows that, as the dose of an antidepressant is increased, the rate of adverse effects and number of treatment dropouts also increase. The question is what happens to treatment response rates with increasing dose? Basic pharmacology teaches us to expect a dose-response relation. Unfortunately, treatment dropouts cloud what should be a simple issue, and alternative analyses lead to conflicting conclusions. The percentage of patients showing improvement to a fixed dose of antidepressant is usually expressed only for patients who complete the protocol. In this review, the response rate for protocol completers rose from 60% at low dose to 76% for the highest doses. Emphasis, however, was placed on an intention-to-treat analysis. Response rates were calculated as the proportion responding after randomisation: all dropouts counted as treatment failures. This analysis resulted in reasonably similar response rates for all doses. The authors conclude that no dose-effect relation exists and that low doses are as effective as higher doses. These conclusions are inconsistent with much current clinical practice and teaching.

The paradox lies in how the factors that cause patients to drop out of clinical trials relate to their treatment response. If patients who drop out tend not to respond anyway, then an intention-to-treat analysis would be the only way to overcome the potential bias of a per-protocol analysis. However, if no relation, or even a positive one, exists between side effects and treatment response, the per-protocol analysis will not be entirely misleading, and a dose-effect relation for antidepressants may exist. It is unclear which of these possibilities is the case: my hunch is that it is the second.

Most clinical trials in depression that are done for regulatory purposes, as in this review, provide an inadequate evidence base for many clinical decisions. Randomised comparisons of protocols of stepped care that are more representative of real clinical practice are needed to help us understand what strategies of treatment are best for patients. Bollini and colleagues are correct, however, in drawing our attention to a law of pharmacology even more fundamental than the dose-response curve. If patients do not take their drugs, we can hardly expect them to derive a benefit from them.

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A modified version
of the abstract and
commentary also
appears in *Evidence-
Based Mental Health*

Effectiveness and adverse effects of various doses of antidepressant drugs*

| Imipramine equivalent doses | Average percentage of patients showing improvement (95% CI) | Average adverse events per week (CI) |
|-----------------------------|---|--------------------------------------|
| Placebo | 35% (25 to 44) | 0.22 (0.13 to 0.33) |
| <100 mg/day | 46% (37 to 55) | 0.22 (0.13 to 0.33) |
| 100 to 200 mg/day | 53% (48 to 59)* | 0.30 (0.21 to 0.39) |
| 201 to 250 mg/day | 46% (35 to 58) | 0.36 (0.23 to 0.52) |
| >250 mg/day | 48% (37 to 60) | 0.48 (0.32 to 0.67) |

*Statistically different from placebo.