Review: benefits of antidepressants over placebo limited except in very severe depression

QUESTION

Question: What are the effects of antidepressant medications across a range of initial symptoms severities in people with depression?

Outcomes: Depression severity measured using the Hamilton Depression Rating Scale (HDRS).

METHODS

Design: Systematic review and individual patient data meta analysis.

Data sources: PubMed, PsycINFO and the Cochrane Library were searched from January 1980 to March 2009. References from meta analyses and reviews were hand searched.

STUDY SELECTION AND ANALYSIS

Placebo-controlled RCTs of US Food and Drug Association-approved antidepressants in adult outpatients with major or minor depressive disorders were included. Studies were excluded if they examined only patients with a specific subtype or severity of depression, compared medication versus placebo for less than 6 weeks, excluded patients on the basis of a placebo washout period, did not use the Hamilton Depression Rating Scale (HDRS), were not published in English, or study authors could not provide individual patient data. Study authors were contacted for individual patient data. Analyses of covariance were used to look at the effect of baseline symptom severity on symptom-change scores with the antidepressant medication versus placebo. The analyses were controlled for the effect of the study whose data were used, and last-observation carried-forward analyses were used for patients who dropped out. Cohen's *d* was used to look at effect sizes among people with different depression severities at baseline: mild-to-moderate (HDRS score ≤18), severe (HDRS score 19–22), or very severe (HDRS score ≥23). An effect size of 0.2 or less is considered small, and an effect size of >0.2 to 0.5 was considered medium. The UK's National Institute of Clinical Excellence (NICE) has set a threshold for clinical significance at an effect size of 0.50 or a drug versus placebo difference of 3 points on the HDRS. A least squares means method was used to estimate at what baseline depression severity score antidepressant medication crossed these thresholds.

MAIN RESULTS

Six RCTs met inclusion criteria – five of major depressive disorder and one of minor depressive disorder. Three RCTs assessed the tricyclic antidepressant imipramine, and the other three assessed the SSRI paroxetine. The studies included 718 patients with a wide range of baseline symptom severity (HDRS scores range 10–39). Both treatment and baseline symptom severity significantly affected change in depression scores ($p<0.001$ for both). There was also significant interaction between baseline severity of depression and treatment. For people with mild-to-moderate or severe depression at baseline, the effect size with antidepressants treatment was small (mild-to-moderate depression: +0.11, 95% CI –0.18 to +0.41; severe depression: +0.17, 95% CI –0.08 to +0.43). For individuals with very severe depression at baseline, the effect size was 0.47 (95% CI 0.22 to 0.71). Estimates of the difference between antidepressants and placebo increased with increasing baseline depression severity. The difference reached NICE's definition of a clinically significant difference at a baseline HDRS score of 25 or 27 depending on which of the two alternative definitions was used (≥3 points on the HDRS or effect size of 0.5, respectively).

CONCLUSIONS

The benefit of antidepressant medication compared with placebo varies, depending on depression severity. In people with mild or moderate or severe depressive symptoms there may be little or no benefit on average. However, the benefit of antidepressant medication over placebo for patients with very severe depression is considerable.

ABSTRACTED FROM

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COMMENTARY

A previous meta-analysis of data submitted to the FDA in the process of obtaining approval for new generation antidepressants failed to show a clinically significant benefit for antidepressant medications, compared to placebo, except for the most extremely depressed patients.[1] Given the controversy that was provoked by that earlier analysis, a conceptual replication was critical.

In the new study, Fournier and colleagues used a different data set, analysed raw data rather than mean scores, and included a broader range of baseline severity. Despite these differences, the results were remarkably consistent. Although drug–placebo differences increased as a function of initially severity, they did not meet the criterion for clinical efficacy set by UK's National Institute for Clinical Excellence[2] for patients with mild, moderate, severe or even very severe depression, crossing the threshold only for those whose baseline scores on the Hamilton Depression Rating Scale (HDRS) was 25 or greater.

The new analysis ought to influence clinical practice profoundly. Data cited by Fournier and colleagues suggest that more than 70% of depressed patients in clinical practice have HDRS scores below 22. That means that the vast majority of depressed patients are being prescribed medications that have negligible benefits to them.

Fortunately, there are effective alternatives.[3] Physical exercise has lasting effects, especially for moderately to severely depressed patients, and if this turns out to also be a placebo effect, it is at least a placebo with an enviable list of side effects. Cognitive-behaviour therapy equals medication effects in the short run and has a substantially lower relapse rate. These alternatives should be attempted prior to antidepressant treatment, which might best be reserved as a last resort.

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Competing interests None.

REFERENCES

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3. **Kirsch I**. *The emperor's new drugs: exploding the antidepressant myth*. London: The Bodley Head, 2009.

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Notes