Effectiveness of antidepressants: meta-analysis of dose-effect relationships in randomised clinical trials

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Authors' objectives

To determine whether high doses of antidepressants (both traditional and newer) are more effective than low doses, and how safety is affected by dose.

Searching

MEDLINE, Current Contents and the Cochrane Controlled Trials Register (CCTR) were searched. The years searched are not given, but some keywords are listed. References of retrieved papers and published literature reviews were examined, and many individual authors were contacted.

Study selection

Study designs of evaluations included in the review

RCTs comparing two different doses of the same drug, with a duration of at least three weeks and more than five patients per treatment arm.

Specific interventions included in the review

Trycyclics (imipramine, clomipramine); tetracyclics (maprotiline); SSRIs (fluoxetine, citalopram, fluvoxamine, minalcipram, sertraline, paroxetine, venlafaxine); MAOIs (isocarboxazid, phenelzine, moclobemide); atypical antidepressants (bupropion, nefazodone, minaprine, rolipram).

Participants included in the review

People with a diagnosis of depression. Of 33 included studies, 25 treated severely depressed patients (diagnosed as having major affective disorder, major depression, endogenous depression or bipolar affective disorder). Two studies had a non-specific diagnosis (eg. depressed mood) and six treated both major and minor depression. Average age ranged from 35 - 54 years (total range 18-89).

Outcomes assessed in the review

Number of patients clinically improved (signified either by a reduction of >50% of total score of Hamilton Rating Scake for Depression (HRSD), by marked- moderate improvement on Clinical Global Impression Scale (CGI) or by lack of relapse of depressive episode). Where a paper reported results from more than one scale, only data from the first scale mentioned in the results section were retained. The second outcome measured was the total number of side effects of any type.

How were decisions on the relevance of primary studies made?

The authors do not state how the papers were selected for the review, or how many of the reviewers performed the selection.

Assessment of study quality

The Jadad checklist was used to assess methodological quality (see Other Publications of Related Interest no.1). Two reviewers scored each paper independently.

Data extraction

Data extraction was independently performed by two reviewers who were blind to the authors and journal title as well as to the type of drug and dose used. Disagreements between reviewers were solved through discussion. Data were extracted on: year of publication, setting, age, gender, diagnosis, duration of treatment, drop-outs, type and dose of

antidepressant, concurrent medication or psychological treatment, outcomes.

Methods of synthesis

How were the studies combined?

The following outcome variables were computed for each study arm: percentage improvement (number clinically improved/number randomised); adverse event rate (((number of adverse drug reactions + number of withdrawals)/number randomised)/number of weeks of treatment). Intention-to-treat analysis was used. Drug doses were standardised with respect to the recommended dose of imipramine (150mg/day), this generated for each drug an equivalence factor by which doses investigated in each trial were multiplied. A fixed effect regression model was used with the dose range of 100-200mg/day as reference to estimate average percentage improvements and average adverse event rates with 95% Cis at five dose levels (placebo; <100mg; 100-200mg; 201-250mg; >250mg).

How were differences between studies investigated?

Antidepressant class, Jadad quality score, proportion of females, duration of treatment (improvement only) and sample size were used as independent factors in the regression model.

Results of the review

Thirty-three studies (n = 6842) were included.

Jadad quality score was 1 for one study, 2 for 11 studies, 3 for 15 studies and 4 for 6 studies.

None of the independent variables considered (antidepressant class, Jadad quality score, proportion of females, sample size, duration of treatment) were significant in the regression analysis and so were not included in the final regression model.

Percentage improvement: placebo 34.8 (95% CI: 25.4-44.3); <100mg 46.0 (95% CI: 36.9-55.1); 100-200mg 53.3 (95% CI: 48.0-58.5); 201-250mg 46.3 (34.9-57.7); >250mg 48.3 (95% CI: 37.0-59.7).

Adverse event rate (events/ week): placebo 0.22 (95% CI: 0.13-0.33); <100mg 0.22 (95% CI: 0.13-0.33); 100-200mg 0.30 (95% CI: 0.21-0.39); 201-250mg 0.36 (0.23-0.52); >250mg 0.48 (0.32-0.67).

Authors' conclusions

The dose level 100-200mg imipramine equivalents showed an average improvement of 53% by intention to treat. Higher doses were not accompanied by increased efficacy while lower doses showed reduction in efficacy. Adverse events significantly increased with dose. With a low dose of antidepressants, clinicians trade off a slightly reduced chance of improvement for a higher chance of avoiding adverse reactions.

CRD commentary

The review question is clearly stated and inclusion criteria are specific. The literature search is not well reported and it is unclear whether there were any language restrictions which could have led to studies being missed. It is unclear whether an attempt was made to find unpublished studies (although authors were contacted); if not, publication bias may result. Study details are not presented. Heterogeneity was investigated by including possible sources in a regression model and these were not found to be significant. Validity was assessed but, again, results are not presented. The authors' conclusions follow from the results but should be treated with some caution given the above limitations.

Implications of the review for practice and research

Research: The authors state that more research is needed on cheaper and, perhaps, more effective interventions aimed at retaining depressed patients on treatment, by managing adverse reactions and improving the therapeutic relationship between patient and physician.

Bibliographic details

Bollini P, Pampallona S, Tibaldi G, Kupelnick B, Munizza C. Effectiveness of antidepressants: meta-analysis of dose-effect relationships in randomised clinical trials. British Journal of Psychiatry 1999; 174: 297-303

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10533547

Other publications of related interest

1. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials 1996;17:1-12.

This additional published commentary may also be of interest. Goodwin GM. Review: lower doses of antidepressant drugs are effective and have fewer adverse effects in depression. Evid Based Med 2000;5:22.

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Subject indexing assigned by NLM

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