Efficacy of antidepressants in juvenile depression: meta-analysis
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CRD summary
This review determined the efficacy of antidepressant therapy in juvenile depression. The authors concluded that antidepressant therapy showed limited efficacy in short-term trials in adolescents and were even less effective in children. The review suffered from some limitations, but the authors’ conclusions seemed to be a reasonable interpretation of the results presented.

Authors’ objectives
To assess the efficacy of antidepressant therapy in juvenile depression.

Searching
MEDLINE, PsychINFO, Cochrane Central Register of Controlled Trials, PsiTri, EMBASE and ClinicalTrials.gov were searched though May 2006 without language restriction. Search terms were not reported. References of relevant papers, pharmaceutical company websites and the UK Committee on Safety of Medicines and the US FDA websites were checked. Experts in the area were contacted in order to identify any additional relevant studies.

Study selection
Prospective, parallel group, double-blind randomised controlled trials (RCTs) that compared any antidepressant with placebo in participants aged 20 years or less diagnosed with major depressive disorder were eligible for inclusion in the review. Participants were required to meet standard diagnostic criteria of DSM-III (or later) or ICD-9/10 for depressive disorder, or have received a diagnosis by clinical or structured diagnostic interview. Interventions were classified as tricyclic antidepressants (TCAs) (amitriptyline, clomipramine, desipramine, imipramine and nortriptyline), serotonin re-uptake inhibitors (SRIs) (RS-citalopram, fluoxetine, paroxetine, sertraline and venlafaxine) and other drugs (mirtazapine, moclobemide, and nefazodone). The mean standardised imipramine equivalent (IMIeq) drug dose was 165mg/day (sd = 48). One trial involved three arms, with paroxetine or imipramine versus placebo. Initial depression severity was considered to be moderate to severe. Mean age of included participants was 13.5 years (range 6 to 20 years). All participants were receiving out-patient treatment for depression. One trial involved adolescents with depression and comorbid alcohol misuse. Eligible outcomes included responder rates, reported as participant counts in each treatment arm, for symptom rating scales. Studies that reported responder rates only as the average percentage change in symptom rating scales were not included.

One reviewer initially screened papers for potential inclusion; two reviewers independently selected studies for inclusion in the review.

Assessment of study quality
The Jadad scale was used to assess the quality of the included studies; each study received a quality score (maximum value of 5). The authors stated neither how the papers were assessed for validity nor how many reviewers performed the validity assessment.

Data extraction
A uniform percentage score of clinical severity (maximum possible score 100%) was calculated for continuous measures of clinical symptom severity. Responder rates were determined for the primary categorical outcome measure defined in each study to distinguish responders and non-responders. Definitions of treatment responder varied across studies, but usually meant at least a 50 per cent improvement of initial ratings of depressive symptom severity. Doses across studies were compared by use of standardised IMIeq daily doses.

One reviewer extracted data from the included studies, which were independently verified by another reviewer; any discrepancies were resolved by consensus.
Methods of synthesis
Studies were combined in a meta-analysis using a fixed effect model. A random effects model was performed if there was evidence of statistical heterogeneity. Summary estimates were reported as rate ratios (RRs) and rate differences (RDs) with 95% confidence intervals (CIs) for all antidepressants combined and for each drug group (TCAs, SRIs and other agents). Subgroup analysis was also performed for different age groups (adolescents, mixed ages and children). Statistical heterogeneity was assessed using the Q and I² statistic. Sensitivity analysis was performed, with the influence of each trial assessed as well as the effect of double inclusion of participants from the three-arm trial. Publication bias was assessed using Begg’s and Egger's tests, funnel plots and meta-regression.

Results of the review
Twenty-nine trials with 30 drug-placebo comparisons were included in the review (n=3,069): 14 comparisons involved TCAs; 12 comparisons involved SRIs; and four comparisons involved other drugs. The median length of treatment duration was eight weeks, with an overall trial experience of approximately 512 person-years. All trials except one were considered to have adequate randomisation and masking. The mean quality score was 2.97 (range 1 to 4). Only six trials presented completed outcomes. All other trials used last outcome carried forward (LOCF).

A moderate effect of treatment with all antidepressants was found compared to placebo (RR 1.22, 95% CI: 1.15, 1.31) and RD 0.107 (95% CI: 0.073, 0.141) with an NNT of 9.35 (95% CI: 7.09, 13.7). No evidence of statistical heterogeneity was found.

When only TCAs were considered, an improvement in favour of antidepressant therapy was found, although this was not statistically significant (RR 1.15 (95% CI: 0.98, 1.34) and RD 0.069 (95% CI: -0.009, 0.146).

Sub-group analysis for SRIs and other drugs found a statistically significant difference in favour of antidepressant therapy compared with placebo. SRIs: RR 1.23 (95% CI: 1.14, 1.33), RD 0.113 (95% CI: 0.072, 0.154), NNT 8.85 (95% CI: 6.49, 13.9). Other drugs: RR 1.27 (95% CI: 1.06, 1.52), RD 0.128 (95% CI: 0.037, 0.219), NNT 7.81 (95% CI: 4.57, 27.0). SRIs showed a slightly higher response rate than TCAs, but overlapping CIs suggested that this difference was not statistically significant. Of the SRIs, fluoxetine showed the greatest pooled efficacy compared to the other SRIs, but overlapping CIs suggested that this was not statistically significant.

Subgroup analysis of age found a statistically significant effect in favour of antidepressant therapy compared with placebo for adolescents only and mixed ages, but not children only. Adolescents only: RR 1.27 (95% CI: 1.15, 1.40), RD 0.120 (95% CI: 0.071, 0.169), NNT 8.33 (95% CI: 5.92, 14.1). Mixed ages: RR 1.19 (95% CI: 1.09, 1.30), RD 0.099 (95% CI: 0.050, 0.148), NNT 10.1 (95% CI: 6.76, 20.0).

Results of the meta-regression indicated that protocol completion versus LOCF and illness severity at baseline were associated with treatment effect (RR). Drug type, sample size, publication year, funding source, exposure weeks, methodological quality, age group, average drug dose and in-patient and out-patient status had only a weak association with drug/placebo response rate ratios.

A funnel plot indicated an asymmetrical distribution of individual rate ratios leaning towards the positive about the pooled value of 1.22, and in a meta-regression analysis the rate ratio was 22 per cent higher in published versus unpublished trials, although unadjusted Begg's and Egger’ tests did not indicate publication bias. The authors suggested that these results indicate there might be some publication bias towards studies favouring active treatment.

Authors' conclusions
Short-term, RCTs of antidepressant therapy found limited clinical efficacy in depression in adolescents, even less efficacy among juvenile patients of mixed ages and possibly yet less effectiveness in children (although this latter group was poorly studied).

CRD commentary
The review question was supported by clear inclusion criteria. Several sources were searched without language restriction for both published and unpublished trials, thereby minimising the likelihood of language of publication bias. Steps were taken to minimise bias and errors in the review process, but the involvement of two independent reviewers
at all stages would have been preferable. Individual study details were available online. Participants from three studies may have been included in the analysis for response to all antidepressants versus placebo more than once, resulting in a loss of independence and a possible exaggeration of effect. Statistical heterogeneity was assessed and a sensitivity analysis conducted. The review suffered from some limitations, but the authors' conclusions seemed to be a reasonable interpretation of the data presented.

**Implications of the review for practice and research**

**Practice:** the authors stated that the limited benefits of antidepressant treatment for depression in children and adolescents had important risk-benefit implications.

**Research:** the authors stated that further trials in children and in severely depressed, hospitalised or suicidal juvenile patients were needed. Trials should also include information on the proportion of participants with mild or moderate depression at baseline. Research goals should include the development of more effective, safe, cost-effective and accessible short- and longer-term treatments for juvenile depression. Specific differences between prepubescent children and adolescents needed to be considered.

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