Clinical response and risk for reported suicidal ideation and suicide attempts in pediatric antidepressant treatment: a meta-analysis of randomized controlled trials

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CRD summary
The authors concluded that antidepressants are effective for paediatric major depressive disorder, obsessive-compulsive disorder (OCD) and non-OCD anxiety disorders and that benefits appear greater than the risk of suicidal ideation and suicide attempt, but benefit-to-risk ratios vary with patient and study characteristics. The conclusion is supported by the results presented, but incomplete reporting of review methods hinders confirmation of the reliability of the conclusions.

Authors' objectives
To evaluate antidepressant treatment for paediatric major depressive disorder (MDD), obsessive-compulsive disorder (OCD) and non-OCD anxiety disorders regarding the efficacy and risks of suicidal ideation and suicide attempt.

Searching
PubMed was searched from 1988 to July 2006; the search terms were reported. In addition, the following sources were screened: reference lists of identified studies; FDA and British Medicines and Healthcare Products Regulatory Agency reports; proceedings of the American Psychiatric Association (2000 to 2005), the American Academy of Child and Adolescent Psychiatry (1998 to 2005) and the New Clinical Drug Evaluation Unit (2001 to 2006); and clinical trial registries. Researchers in the field were also contacted.

Study selection
Study designs of evaluations included in the review
Parallel-group, randomised controlled trials (RCTs) were eligible for inclusion in the review.

Specific interventions included in the review
Studies that compared selective serotonin re-uptake inhibitors and other second-generation agents with placebo were eligible for inclusion. Studies that provided adjunctive cognitive-behavioural therapy to all patients were excluded. Several included studies evaluated fluoxetine; others evaluated paroxetine, sertraline, citalopram, escitalopram, venlafaxine, nefazodone, mirtazapine and fluvoxamine. Most of the studies used a flexible dose. The median treatment duration was 8 weeks for patients with MDD and 11 weeks for patients with OCD and non-OCD anxiety disorders.

Participants included in the review
Studies in children and adolescents (aged less than 19 years) with MDD, OCD or non-OCD anxiety disorders were eligible for inclusion. Studies that only included patients who had responded to treatment were excluded, as were studies of patients with anxiety-related conditions other than separation, social or generalised anxiety disorder. Most of the included studies were conducted in the USA.

Outcomes assessed in the review
Studies that provided efficacy or treatment-emergent data on suicidal ideation/suicide attempt for both treatment groups were eligible for inclusion. The primary review efficacy outcomes were (study-defined) treatment response and a predefined scalar measure of change in symptoms from baseline. The primary harms outcome was suicidal ideation/suicide attempt; this was based either on Food and Drug Administration (FDA) ratings or assessed by the reviewers. Most of the included studies used the Children's Depression Rating Scale-Revised, the Children's Yale-Brown Obsessive Compulsive Scale or the Pediatric Anxiety Rating Scale.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
Two reviewers assessed the validity of published studies with adequate data using criteria described by Detsky et al.
Any disagreements were resolved by consensus.

**Data extraction**
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction. For each study, response rates were extracted for the treatment and control groups, and the Mantel-Haenszel risk difference (RD), number-needed-to-treat (NNT) and Hedges g effect size for scalar measures of efficacy were calculated with 95% confidence intervals (CIs) (see Other Publications of Related Interest). Hedges g was also calculated for dichotomous data (transformation method reported). For most studies, data on suicidal ideation/suicide attempt were extracted from the FDA report (see Other Publications of Related Interest), otherwise data were obtained from the principal study researcher or study reports.

**Methods of synthesis**

**How were the studies combined?**
The studies were grouped by indication for drug treatment (MDD, OCD and non-OCD anxiety disorder). A pooled RD with 95% CI was calculated for dichotomous data using the random-effects DerSimonian and Laird model, in addition to the pooled Hedges g effect. Pooled random-effects mean differences were calculated with 95% CIs for continuous data for scalar measures of efficacy and expressed as Hedges g. Where statistically significant differences between treatments were found, the NNT and number-needed-to-harm (NNH) were calculated. Publication bias was assessed using a funnel plot and tested using an adjusted rank correlation test and a regression test to measure asymmetry.

**How were differences between studies investigated?**
Statistical heterogeneity was assessed using the Cochran Q statistic (p=<0.10) and the I-squared statistic. Results from random-effects and fixed-effect models were compared. The influence of individual studies was assessed by repeating the analysis after omitting each study in turn. Pooled results were compared with the FDA report results. An exact homogeneity test was used to examine the influence of continuous variables (study quality, number of treatment sites, proportions of female patients and duration of illness at baseline); statistically significant effect modifiers were then dichotomised and reanalysed as categorical variables. The influence of trial-level variables was also examined (publication status, funding source, study location, drug class and placebo run-in period). One small study with a very large treatment effect was excluded from all regression and moderator efficacy analyses.

**Results of the review**
Twenty-seven RCTs (n=5,310) were included. Of these, 15 RCTs evaluated treatment effects in patients with MDD (n=3,430), 6 RCTs evaluated patients with OCD (n=718) and 6 RCTs evaluated patients with non-OCD anxiety disorders (n=1,162).

The studies were generally of good quality; the median Detsky score was 0.88 for the 23 trials with adequate data. Methodological problems included a lack of strict intention-to-treat analysis and inadequate reporting of randomisation methods and exclusions.

**MDD.**
Antidepressants were associated with a significantly increased treatment response rate compared with placebo, 61% versus 50%; the RD was 11% (95% CI: 7.1, 14.9; 13 trials) and the NNT was 10 (95% CI: 7, 15).

Antidepressants were associated with a non-statistically significant increased risk of suicidal ideation/suicide attempt compared with placebo, 3% versus 2%; the RD was 0.9% (95% CI: -0.1, 1.9) and the NNH was 112.

**OCD.**
Antidepressants were associated with a significantly increased treatment response rate compared with placebo, 52% versus 32%; the RD was 20% (95% CI: 13, 26.6; 6 trials) and the NNT was 6 (95% CI: 4, 8).

Antidepressants were associated with a non-statistically significant increased risk of suicidal ideation/suicide attempt.
compared with placebo, 1% versus 0.3%; the RD was 0.5% (95% CI: -1.2, 2.2) and the NNH was 200.

Non-OCD anxiety disorders.

Antidepressants were associated with a significantly increased treatment response rate compared with placebo, 69% versus 39%; the RD was 37.1% (95% CI: 22.5, 51.7; 6 trials) and the NNT was 3 (95% CI: 2, 5). All studies showed benefit with antidepressant use but significant heterogeneity was found (p<0.001).

Antidepressants were associated with a non-statistically significant increased risk of suicidal ideation/suicide attempt compared with placebo, 1% versus 0.2%; the RD was 0.7% (95% CI: -0.4, 1.8) and the NNH was 143.

There was an increased RD of suicidal ideation/suicide attempt across all trials and indications for drug versus placebo (RD 0.7%, 95% CI: 0.1, 1.3; 27 trials). There were no completed suicides in any of the studies.

There was no evidence of publication bias for any of the medical conditions.

**Authors' conclusions**

Antidepressants are more effective than placebo for children and adolescents with MDD, OCD and non-OCD anxiety disorders. The response to treatments is greatest for patients with non-OCD anxiety disorders, intermediate for OCD and modest for MDD. The benefits appear to be greater than the risk of suicidal ideation/suicide attempt across all three conditions, but the benefit-to-risk ratios vary with diagnosis, age, duration of illness and study characteristics.

**CRD commentary**

The review addressed a clear question that was defined in terms of the participants, intervention, outcomes and study design. The authors undertook an extensive search, albeit in selected sources (other electronic databases such as EMBASE or PsycINFO were not searched), and made attempts to minimise publication bias, but it was not clear whether any language restrictions had been applied. Methods were used to minimise reviewer errors and bias in the assessment of validity, but it was not clear whether similar steps were taken in the study selection and data extraction processes. Validity was assessed and some methodological problems were reported. The studies appear to have been appropriately pooled using several different methods of meta-analysis, statistical heterogeneity was assessed, and the influence of various factors on the results was examined and discussed. The conclusion is supported by the results presented. However, incomplete reporting of the review methods makes it difficult to confirm the reliability of the authors' conclusion.

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

Practice: The authors stated that the review supports the 'cautious and well-monitored use of antidepressant medication as one of the first-line treatments'. The choice of treatment should be made after discussion between clinicians, family and the patients.

Research: The authors stated the need for mandatory registration of clinical trials and the full and public reporting of relevant baseline characteristics and its effect on outcome data. Research is required to develop efficient methods for monitoring children and adolescents taking antidepressants in order to evaluate clinical response and adverse effects. Assays of drug and metabolites could help identify nonadherent and nonresponsive patients.

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