Tricyclic antidepressants for attention deficit hyperactivity disorder (ADHD) in children and adolescents.


Abstract
BACKGROUND: Attention deficit hyperactivity disorder (ADHD) is a chronic neurodevelopmental disorder of childhood onset, which may persist into adulthood. ADHD has a significant impact on a child's daily life, affecting relationships and academic performance. Its core symptoms include developmentally inappropriate levels of inattention, hyperactivity, and impulsive behaviour. Tricyclic antidepressants (TCAs) are sometimes used as second line of treatment in the reduction of ADHD symptoms in children and adolescents with ADHD. However, their efficacy is not yet known.

OBJECTIVES: To assess the efficacy of TCAs in the reduction of ADHD symptoms within the broad categories of hyperactivity, impulsivity, and inattentiveness in young people aged 6 to 18 years with established diagnoses of ADHD.

SEARCH METHODS: On 26 September 2013, we searched CENTRAL, Ovid MEDLINE, Embase, PsycINFO, CINAHL, seven other databases, and two trials registers. We also searched the reference lists of relevant articles, and contacted manufacturers and known experts in the field to determine if there were any ongoing trials or unpublished studies available.

SELECTION CRITERIA: Randomised controlled trials (RCTs), including both parallel group and cross-over study designs, of any dose of TCA compared with placebo or active medication in children or adolescents with ADHD, including those with comorbid conditions. DATA COLLECTION AND ANALYSIS: Working in pairs, three review authors independently screened records, extracted data, and assessed trial quality. We calculated the standardised mean differences (SMD) for continuous data, the odds ratio (OR) for dichotomous data, and 95% confidence intervals (CIs) for both. We conducted the meta-analyses using a random-effects model throughout. We used the Cochrane 'Risk of bias' tool to assess the risk of bias of each included trial and the GRADE approach to assess the quality of the body evidence.

MAIN RESULTS: We included six RCTs with a total of 216 participants. Five of the six trials compared desipramine with placebo; the remaining trial compared nortriptyline with placebo. One trial compared desipramine with clonidine and placebo, and another compared two TCAs (desipramine and clomipramine) with methylphenidate and placebo. Of the six trials, one RCT primarily assessed the efficacy of TCA in children with ADHD and comorbid tic or Tourette disorder, and another one trial was in children with comorbid tic disorder. RCTs that met our inclusion criteria varied both in design and quality, and none were free of bias. The quality of the evidence was low to very low according to our GRADE assessments. TCA outperformed placebo regarding the proportions of patients achieving a predefined improvement of core ADHD symptom severity (OR 18.50, 95% CI 6.29 to 54.39, 3 trials, 125 participants, low quality evidence). In particular, there was evidence that desipramine improved the core symptoms of ADHD in children and adolescents as assessed by parents (SMD -1.42, 95% CI -1.99 to -0.85, 2 trials, 99 participants, low quality evidence), teachers (SMD -0.97, 95% CI -1.66 to -0.28, 2 trials, 89 participants, low quality evidence), and clinicians (OR 26.41, 95% CI 7.41 to 94.18, 2 trials, 103 participants, low quality evidence). Nortriptyline was also efficacious in improving the core symptoms of ADHD as rated by parents (SMD -0.90, 95% CI -1.40 to -0.40, 1 trial, 68 participants, very low quality evidence). Desipramine appeared more efficacious than clonidine in reducing ADHD symptoms as rated by parents (SMD -0.90, 95% CI -1.40 to -0.40, 1 trial, 68 participants, very low quality evidence) in participants with ADHD and
comorbid tics or Tourette syndrome. Although this Cochrane Review did not identify serious adverse effects in patients taking TCAs, it did identify mild increases in diastolic blood pressure and pulse rates. Also, patients treated with desipramine had significantly higher rates of appetite suppression compared to placebo whilst nortriptyline resulted in weight gain. Other reported adverse effects included headache, confusion, sedation, tiredness, blurred vision, diaphoresis, dry mouth, abdominal discomfort, constipation, and urinary retention.

AUTHORS' CONCLUSIONS:
Most evidence on TCAs relates to desipramine. Findings suggest that, in the short term, desipramine improves the core symptoms of ADHD, but its effect on the cardiovascular system remains an important clinical concern. Thus, evidence supporting the clinical use of desipramine for the treatment of children with ADHD is low.