A meta-analysis of clonidine for symptoms of attention-deficit hyperactivity disorder
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Authors' objectives
To review the literature on the clinical use of clonidine to treat symptoms of attention-deficit hyperactivity disorder (ADHD).

Searching
The following sources were searched: MEDLINE from 1980 to 1999, PsycINFO from 1984 to 1999, Currents Contents (Social and Behavioural Sciences) from 1996 to 1999, and Currents Contents (Clinical Medicine) from 1996 to 1999. The keywords included the following terms: 'clonidine' alone or in combination with 'attention deficit', 'hyperactivity', 'conduct', 'disruptive behavioural', 'Tourette's', 'tic', 'autism', 'developmental delay' or 'posttraumatic distress disorder'. Non-peer-reviewed research reports, book chapters, chapter bibliographies, and individual report references were also included in the search. The searches were limited to English language publications.

Study selection
Study designs of evaluations included in the review
All study designs involving more than one patient were eligible for inclusion.

Specific interventions included in the review
Clonidine, in daily doses ranging from 0.10 to 0.24 mg/day for a duration of 3 to 51 weeks. In one trial patients received concomitant clonazepam, and in another, 4 patients received concomitant stimulant medication.

Participants included in the review
Children and adolescents aged up to 18 years who exhibited symptoms of ADHD were included. Studies reporting mixed samples of children, adolescents and adults were eligible for inclusion if the mean sample age was less than 18 years. Co-morbid diagnoses included developmental delay, tic and conduct disorder.

Outcomes assessed in the review
Studies were eligible for inclusion if they measured an outcome for the effect of clonidine on ADHD features. The included studies used rating scales to assess ADHD.

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
Validity was assessed using the following criteria: blindness of raters (none, single-, or double-blind), random assignment to group, crossover or parallel group design, placebo control, presence of drug-free washout period, placebo-controlled wash-in phase, prospective design, and the use of a validated scale specific for ADHD. Studies could be awarded a maximum of 8 points. Studies with scores greater than 6 were identified as having stronger-than-average methodology, whilst those scoring less than 6 were identified as having weaker-than-average methodology. Two reviewers conjointly assigned points for the quality of methodological design. Any discrepancies in the ratings were identified and discussed, specific articles were re-reviewed, and final conclusions were agreed upon by consensus.

Data extraction
The authors do not state how the data were extracted for the review, or how many of the reviewers performed the data extraction. Data were extracted on: study design, random assignment to group (plus or minus), method rating on a
scale of 0 to 8), mean age of participants (years), sample size and number of placebo controls, daily dose (mg/day), concomitant medication, duration of trial (weeks), and co-morbid diagnoses.

**Methods of synthesis**

How were the studies combined?
The effect size was calculated for each study using Hedge's g (see Other Publications of Related Interest no.1). This was then adjusted for potential bias associated with the original estimate difference between conditions normalised on the basis of the standard deviation of the measure. Analyses were conducted with both unweighted effect sizes and with effect sizes weighted by sample variance (see Other Publications of Related Interest no.2).

How were differences between studies investigated?
Homogeneity was tested using the chi-squared test. In addition, sensitivity analyses were undertaken using cluster analysis to determine which studies provided homogeneous subgroups of effect sizes (see Other Publications of Related Interest no.2).

**Results of the review**

Eleven studies (n=150) were included in the review: 8 randomised controlled trials (4 parallel group trials and 4 crossover trials) and 3 uncontrolled test-retest studies.

Ratings for methodology.

Scores for the included studies ranged from 1 to 8. Eight studies were rated to be of stronger-than-average design, and 3 of less-than-average design.

Clinician ratings (5 studies, n=61).

A test of homogeneity of effect sizes for these 5 studies was significant (chi-squared 49.88, d.f.=5, p<0.0001). A cluster of 3 studies (n=36) with methodology ratings greater than or equal to the average gave a weighted Hedge's g of 0.43 (z=1.73, p<0.05).

Parent ratings (9 studies, n=125).

A test of homogeneity of effect sizes for these 9 studies was significant (chi-squared 79.16, d.f.=8, p<0.0001). Cluster analysis identified 3 clusters, of which the largest included 6 studies all with methodology scores greater than 6. For this group of 6 studies (n=84), the weighted adjusted average Hedge's g was 0.75 (z=4.58, p<0.0001).

Teacher ratings (6 studies, n=89).

A test of homogeneity of effect sizes for these 6 studies was significant (chi-squared 124.09, d.f.=5, p<0.0001). A cluster of 3 studies (n=48) with stronger-than-average methodology ratings gave a weighted Hedge's g of 0.56 (z=2.68, p<0.004).

Overall ratings from all sources.

The test of homogeneity of effect sizes for overall ratings from all 11 studies was significant (chi-squared 141.95, d.f.=10, p<0.0001). Six studies (n=84), with stronger-than-average methodology, gave a weighted average Hedge's g of 0.58 (95% confidence interval: 0.27, 0.89, p<0.001, z=3.66).

Side-effects.

The most commonly reported side-effects were sedation in 9 out of 10 studies, and irritability in 6 out of 10 studies.

**Authors' conclusions**
Clonidine may be an effective second-tier treatment for symptoms of ADHD, but it has an effect size less than that of stimulants. The clinical use of clonidine is associated with many side-effects.

CRD commentary
The methodological quality of this review was generally fair but a number of flaws were apparent.

The inclusion criteria for the review were poorly reported. It was difficult to identify the actual outcomes included in the review as no details were provided of how the outcomes were defined or measured. Additionally, no clear definition of ADHD was reported, and studies that did not use a validated scale specific for ADHD were still eligible for inclusion. The authors carried out a comprehensive search of the literature but by only including English language publications, some important studies may have been missed. No details were reported on how the studies were selected and the data extracted, or how many reviewers performed these processes. The authors undertook an appropriate validity assessment of the studies. However, it was not only rather simplistic to subdivide the studies into only two groups ('greater-than-average' and 'lower-than-average'), but it was also unclear what constituted an 'average' study. The results of the review were not reported clearly and some study characteristics were omitted from the tables; in particular, these included outcome, definition of ADHD and the number of drop-outs. The results reported in the text differed from those presented in the tables, and 95% confidence intervals were only reported for one outcome, in the abstract.

The conclusion that the effect size for clonidine was less than that for stimulants does not follow directly from the information presented in the review.

Implications of the review for practice and research
Practice: The authors state that this review provides some support for the clinical use of clonidine to treat ADHD. Doses of 0.1 to 0.3 mg per day appear to have moderate treatment effects for the common symptoms of ADHD in children and adolescents. Clinicians should be aware that the efficacy of clonidine is less than that for established treatment stimulants, and that treatment is associated with many side-effects.

Research: The authors state that future research designs should use an expanded array of multisource, multimethod outcome measures, with adequate sample size, random assignment to treatment groups, and comparison with placebo controls.

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Other publications of related interest

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.