Authors' objectives
To determine:


2. Whether combined interventions are more effective than individual interventions.

Searching
MEDLINE (from 1966), CINAHL (from 1982), HEALTHStar (from 1975), PsycINFO (from 1984) and EMBASE (from 1984) were searched. The searches were completed in November 1997 using the terms 'behavioural symptoms', 'attention-deficit disorder with hyperactivity', 'attention-deficit', 'hyperactivity', 'cognition disorders', 'minimal brain damage', 'minimal brain dysfunction', 'hyperkinetic syndrome', 'hyperkinetic reaction', 'impulsivity or inattention' and 'random', 'clinical trial', 'comparative', 'case control', or 'cohort'. Also searched were: The Cochrane Library (issue 4, 1997), the reference lists of any eligible article identified, websites of organisations funding research on the treatment of ADHD and files of members of the research team and partner organisations. Studies published in peer reviewed journals in any language, as a full report, were eligible for inclusion.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs). Non-RCT studies were included if they met all of the other inclusion criteria and if they evaluated adverse effects associated with treatment for more than 12 weeks and included more than 10 patients.

Specific interventions included in the review
Drug-to-Drug Comparisons: studies that included one of the following head-to-head comparisons:

1. Stimulants (methylphenidate, dextroamphetamine or pemoline) vs. stimulants (trials comparing the same drug were included if different formulations of different enantiomers).

2. Stimulants vs. tricyclic antidepressants.

3. Stimulants vs. clonidine, buproprion, or selective serotonin-reuptake inhibitors were eligible for inclusion.

Tricyclic Antidepressants vs. Placebo: Studies that compared placebo with amitriptyline, imipramine, or desipramine.

Drug vs. Nondrug Studies: studies in which:

1. One of the study arms included only a stimulant drug.

2. One or more of the control arms included other modes of intervention such as behaviour modification, dietary interventions, or other psychosocial interventions.

Combination Therapy: studies in which:

1. One of the study arms included two or more interventions given in combination.

2. One of the study arms included a stimulant.

Long-Term Therapy: studies that evaluated treatment for 12 weeks or more in all study arms.
Specific interventions included: amphetamine, attention control/child training, behaviour modification, bibliotherapy protocol, bupropion, caffeine, child training, chlorpromazine, clonidine, cognitive behavioural therapy, desipramine, dexamphetamine, EEG biofeedback, efamol, haloperidol, hydroxyzine, imipramine, L-amphetamine, lithium carbonate, methylphenidate, nicotine, nothing (e.g. waiting lists), parent training, pemoline, phenylalanine, pinodol, placebo, racemic amphetamine, seconobarbitol, selegiline, supportive therapy and thioridazine.

Participants included in the review
Both adults and children suffering from ADHD. For treatment of ADHD in adults, a study was included if treatments were evaluated in patients older than 18 years of age. Studies that included conditions other than ADHD were included only if they provided separate analyses for patients with ADHD.

Outcomes assessed in the review
Outcomes of interest extracted were: abdominal pain; achievement tests; aggressiveness; anorexia; anxiety; arithmetic; behaviour disturbances; CD; core symptoms; crying; decreased appetite; depression; disturbed sleep; emotional; fatigue/tiredness; global mood; global side effects; global symptoms; grades; growth; headache; height; hyperactivity; impulsivity; inattention; increased appetite; interaction with family; interaction with friends; irritability; listening; motor tics; nausea; nightmares; ODD; reading; performance; sadness; self-control; self-esteem; sleep disorder - insomnia; sleep disorder - sleep; social competence; somatic effects; spelling; verbal; weight; weight gain; and weight loss.

The following tests were used: ACTeRS; ADHD rating scale; Beck Depression Inventory; Behaviour Problem Checklist; Brief Psychiatric Rating Scale; CGI - Global Improvement; CGI - Severity of Illness; Child Psychological Rating; Children's Checking Task; Children's Depression Inventory; Clinical Global Improvement; Conners Child/Self; Conners Parent Rating Scale; Conners Teacher/Spouse; CPT; DETROIT13; DETROIT16; DETROIT6; DTS; Durrell Anal. Reading; EFT; Gates McGinty Test; Global Assessment Scale; HAM-A; Hamilton Psychiatric Rating - Depression; How I Feel; Humphries Self-control - Teacher; KBIT; MFFT; Other Clinician Report; Other Parent report; Other Teacher Report; Peterson Quay Checklist; PGS; Physician Global Assessment of Change; Piers Harris Scale; POMS; PTSR; Report Only; SNAP; STESS; STM Task; Unspecified reaction performance; Werry Weiss Activity Scale; Weschler; and WRAT.

How were decisions on the relevance of primary studies made?
Hard copies of studies were obtained and independently assessed by two members of the research team who then decided, by consensus, whether to include the study.

Assessment of study quality
The quality of each study was assessed using a Quality Assessment Scale (see Other Publications of Related Interest no.2). Studies were given a score of 1 point for each of the criteria they satisfied. The scoring range was 0-5, a score of less than 3 was deemed to be poor quality. Two reviewers performed the quality assessment and disagreements were resolved by consensus and by referring to the information in the original report.

Data extraction
Data extraction forms were specially developed and tested. Two reviewers extracted data independently from each of the full reports. Any differences were resolved by consensus and by referring to the information in the original report. Any differences that could not be resolved by the two reviewers who extracted the data were resolved by the task order leader or by a member of the local research team. The original reports were not masked. The information extracted addressed 41 different aspects of the studies which were selected by the team members a priori. Aspects assessed included: evidence of bias, patient characteristics, links to pharmaceutical or related industry, sampling issues, diagnosis-related issues, and treatment-related issues.

Methods of synthesis
How were the studies combined?
The authors combined studies in a qualitative synthesis. Evaluation of the overall quantity and quality of the data available led to the conclusion that meta-analysis would be inappropriate due to substantial clinical heterogeneity across
the studies (e.g. therapies evaluated, patient populations, duration), inconsistency in outcome measurements, low methodological quality, and incomplete data reporting. Study results were grouped into seven categories.

How were differences between studies investigated?
The authors do not describe a formal method for assessing heterogeneity but state that 'substantial clinical heterogeneity' was found.

Results of the review
One hundred and thirty-five RCTs and 1 non-RCT.

The average quality score was 2 out of 5 points. Only one study was given the maximum quality score of 5 points.

Drug vs. Drug comparisons (n = 22 RCTs): few, if any, differences among methylphenidate (MPH) and dextroamphetamine (DEX), and pemoline; studies comparing stimulants with tricyclic antidepressants were inconclusive.

Drug vs. non-drug studies (n = 6 RCTs): stimulants, particularly MPH, may be more effective than non-pharmacological interventions.

Combination therapy (n = 20 RCTs): no additional beneficial effects for combination therapies were shown.

Tricyclic antidepressants vs. placebo (n = 9 RCTs): desipramine may be more effective than placebo; no consistent effect was shown for imipramine.

Long term therapy (>=12 weeks) (n = 14 RCTs (13 in school children and 1 in adults)): a trend to general improvement regardless of treatment was found, but the length of follow-up was inadequate. MPH may reduce behavioural disturbance in children with ADHD while it is taken. Academic performance does not appear to be improved with stimulants.

Treatment of ADHD in adults (n = 12 RCTs): for MPH vs. placebo, the results were contradictory. Antidepressants may be effective in adults, but no beneficial effect was seen with pemoline, nicotine, or phenylalanine compared with placebo.

Adverse effects of drug therapy (n = 28 RCTs, 1 non-RCT): many of the side effects associated with stimulant use appear to be relatively mild and of short duration and to respond to dosing or timing adjustments. Data are inadequate on the long-term effects and severity of adverse effects of most interventions. No comparative studies were identified with data on important adverse effects of interest, including potential for abuse of stimulants, liver toxicity due to pemoline, or major arrhythmia with tricyclic antidepressants.

Authors' conclusions
Studies on ADHD have low reporting quality, methodological flaws, and heterogeneity across outcome measures and tests.

CRD commentary
Overall this was a high quality systematic review. Although the scope of the review question was broad, each category contained well defined inclusion criteria. The search undertaken was comprehensive and assessment of study quality was good. Only published studies were included and so the results may be subject to selection bias. The data was pooled in a narrative synthesis and this was appropriate given the nature of the evidence.

The authors provide sound conclusions from the evidence and provide detailed implications for further research.

Implications of the review for practice and research
Practice: The authors do not state any implications for practice.

Research: The authors state that the quality of study designs and reports need to be improved, and that larger studies with more rigorous design and longer term follow-up are needed to establish the effectiveness and adverse effects of most interventions in both adults and children.

**Bibliographic details**

**Original Paper URL**
http://www.ahrq.gov/clinic/epcsums/adhdsst.htm

**Other publications of related interest**

This additional published commentary may also be of interest. Margo G. Review: pharmacological interventions are more effective than non-pharmacological for attention deficit hyperactivity disorder. Evid Based Med 2000;5:179.

**Indexing Status**
Subject indexing assigned by CRD

**MeSH**
Adrenergic Uptake Inhibitors /adverse effects /therapeutic use; Adult; Antidepressive Agents, Tricyclic /adverse effects /therapeutic use; Attention Deficit Disorder with Hyperactivity /drug therapy /therapy; Central Nervous System Stimulants /adverse effects /therapeutic use; Child; Child Behavior /drug effects; Combined Modality Therapy; Desipramine /adverse effects /therapeutic use; Dextroamphetamine /adverse effects /therapeutic use; Evidence-Based Medicine; Follow-Up Studies; Imipramine /adverse effects /therapeutic use; Methylphenidate /adverse effects /therapeutic use; Nicotine /therapeutic use; Nicotinic Agonists /therapeutic use; Pemoline /adverse effects /therapeutic use; Phenylalanine /therapeutic use; Placebos; Randomized Controlled Trials as Topic; Safety; Treatment Outcome

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