Meta-analysis: treatment of attention-deficit/hyperactivity disorder in children with comorbid tic disorders

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CRD summary
The authors concluded that methylphenidate, alpha-2 agonists, atomoxetine and desipramine were efficacious for treatment of attention deficit and hyperactivity disorder with comorbid tics. The authors’ conclusions were based on limited evidence from a few generally small short-term studies of uncertain quality. This and a limited search and inadequate reporting of review methods mean that the conclusions may not be reliable.

Authors' objectives
To evaluate the efficacy of different medications for the treatment of attention deficit and hyperactivity disorder (ADHD) and tic symptoms in children with both Tourette’s syndrome and ADHD.

Searching
PubMed was searched. Search terms were reported, but search dates were not. Reference lists of included studies, reviews and meta-analyses were screened for further published and unpublished studies.

Study selection
Double-blind randomised controlled trials (RCTs) were included if they compared a medication given for at least one week against placebo in children and adolescents (<18 years of age) diagnosed with ADHD or a hyperkinetic disorder and a tic disorder using recognised criteria. Primary review outcomes were mean change in rating scales for tic and ADHD severity (acceptable scales for both these conditions were stated). Secondary outcomes were effects on inattention and hyperactivity/impulsivity symptoms of ADHD separately. Side effects were assessed.

Included studies evaluated: methylphenidate derivative (methylphenidate); amphetamine derivatives (dexamphetamine); atomoxetine; alpha-2 agonists (clonidine and guanfacine); tricyclic antidepressants (desipramine); and deprenyl. Most trials evaluated a single medication; one trial evaluated a combination of agents. Patient age ranged from five to 17.5 years. Percentage of males ranged from 80% to 100%. Duration of included interventions ranged from two to 18 weeks; most lasted eight weeks or less. Studies were published between 1992 and 2007.

Two reviewers selected studies; it was unclear whether they did this independently.

Assessment of study quality
The authors did not state that they assessed validity.

Data extraction
Data were extracted on mean differences and standard deviations to enable calculation of standardised mean differences (SMDs) and 95% confidence intervals (CIs). For cross-over studies, mean differences and standard deviations were calculated where individual patient data were available for the baseline and cross-over period; otherwise SDs of paired observations were estimated from reported statistics. Adverse event rates were extracted. Authors were contacted for additional data, but none was forthcoming.

The authors did not state how many reviewers performed data extraction.

Methods of synthesis
For each type of medication, pooled SMDs with 95% confidence intervals (CI) were calculated using a random-effects model; results were reported as effect sizes (ES). Heterogeneity was assessed using the I² statistic and was explored by examining the influence of study duration, drug dosage and formulation of medication. The possibility of publication bias was reported as being explored using a funnel plot

Results of the review
Nine RCTs were included (n=477): five cross-over and four parallel-group RCTs. Sample size ranged from 11 to 148. Six studies involved fewer than 50 patients.

**Methylphenidate derivatives:** Methylphenidate was associated with a statistically significant improvement in ADHD symptoms compared to placebo (ES 0.73, 95% CI 0.53 to 0.94; three RCTs). There was no significant difference in pooled effect size for tic symptoms (four RCTs). There was significant heterogeneity in the outcome of tic symptoms ($I^2=56.8\%$). Side effects were not well described in any of the studies.

**Amphetamine derivatives:** Dexmethylphenidate was associated with a statistically significant increase in tic severity (ES -0.59, 95% CI -1.06 to -0.13; one cross-over study, n=12). No changes in ADHD severity were reported.

**Alpha-2 agonists:** Alpha-2 agonists were associated with a statistically significant improvement in tic severity (ES 0.74, 95% CI 0.44 to 1.04; two studies) and ADHD symptoms (ES 0.61, 95% CI 0.32 to 0.90; three studies). There was increased sedation compared to placebo (41% to 48% versus 6%).

**Tricyclic antidepressants:** Desipramine was associated with a statistically significant improvement in ADHD symptoms compared to placebo (ES 0.80, 95% CI 0.02 to 1.57; significant heterogeneity was found, $I^2=86\%$; two studies). There was no significant difference in tic severity (one study). Adverse effects were more common in desipramine compared to placebo groups in both studies. One trial reported a significant increase in diastolic blood pressure and pulse rate in the desipramine group compared to the placebo group.

**Atomoxetine:** Atomoxetine was associated with a statistically significant improvement in ADHD symptoms (ES 0.51, 95% CI 0.27 to 0.74; one study, n=148) and tic severity (ES 0.32, 95% CI 0.09 to 0.56; one study, n=148). Nausea and decreased appetite were more common in atomoxetine compared to groups (16% versus 1% to 3%).

**Deprenyl:** There was no significant differences between deprenyl and placebo in ADHD, tic severity and adverse effects (one study).

**Combination treatments:** Clonidine plus methylphenidate was associated with a statistically significant improvement in ADHD symptoms (ES 1.09, 95% CI 0.72 to 1.45; one study, n=103) and tic severity (ES 0.75, 95% CI 0.38 to 1.12; one study). Sedation was more common in combination treatment groups compared to placebo (21% versus 6%).

Where possible, results of effects of different medications on inattention and hyperactivity/impulsivity symptoms were reported.

**Authors' conclusions**
Methylphenidate seemed to offer the greatest and most immediate improvement of ADHD symptoms and did not seem to worsen tic symptoms. Alpha-2 agonists offered the best combined improvement of both tic and ADHD symptoms. Atomoxetine and desipramine offered additional evidence-based treatments of ADHD in children with comorbid tics. Supratherapeutic doses of dextroamphetamine should be avoided.

**CRD commentary**
The review question was clearly stated and inclusion criteria were appropriately defined. Limiting the search to one database plus references raised potential for publication bias and the omission of other relevant studies. The authors stated that unpublished studies identified through references were eligible, but their search was not adequate to minimise publication bias. Results of the authors' assessment of publication bias were not reported. It was unclear whether attempts were made to minimise language bias. It was unclear whether adequate steps were taken to minimise reviewer errors and bias during study selection and data extraction.

Only double-blind RCTs were included, but no other aspect of study validity was assessed and so results from these studies and any synthesis may not be reliable. Little information was provided about participants, which made it difficult to judge the generalisability of review findings. Appropriate methods were used for meta analyses. Heterogeneity was assessed. The authors' conclusions were based on limited evidence from a few generally small short-term studies of uncertain quality. This and a limited search and inadequate reporting of review methods mean that the conclusions may not be reliable.
Implications of the review for practice and research

**Practice:** The authors stated that caution was required when using clonidine plus methylphenidate to treat children with known cardiac defects and that supratherapeutic doses of dextroamphetamine should be avoided.

**Research:** The authors did not state any implications for research.

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