Psychopharmacology and aggression - 1: a meta-analysis of stimulant effects on overt/covert aggression-related behaviors in ADHD.

Authors' objectives
To determine by meta-analysis the effect size for stimulants on overt and covert aggression-related behaviours in children with attention-deficit hyperactivity disorder (ADHD), separately from stimulant effects on the core symptoms of ADHD.

Searching
MEDLINE and PubMed were searched from 1970 to 2001 using keywords that were reported in the paper. The bibliographies of relevant journals were also searched. The searches were limited to English language studies. Only studies published in a peer-reviewed scientific journal were included.

Study selection
Study designs of evaluations included in the review
Studies using a placebo control, either in a crossover or parallel-group methodological design, were eligible for inclusion. Open studies, case-reports and review articles were excluded.

Specific interventions included in the review
Stimulants for aggression-related behaviours in children with ADHD. The drug types investigated by the included studies were methylphenidate, amphetamine, and pemoline.

Participants included in the review
Studies involving youths with ADHD were eligible for inclusion. The studies were required to have a mean sample age of less than 18 years. Aggression-related behaviours were categorised as overt or covert, where overt aggression was defined as aggression resulting in a direct confrontation with the environment, and covert aggression was defined as aggression that is furtive and hidden from the environment.

Outcomes assessed in the review
Studies reporting quantitative data on stimulant effects for aggression-related behaviours within the context of ADHD were eligible for inclusion. The studies were required to use a rating scale or method of observation to assess aggression-related behaviours. Studies reporting only included the effects of stimulants on core symptoms of ADHD were excluded.

How were decisions on the relevance of primary studies made?
The authors did not specifically state how the papers were selected for the review. However, it was stated that studies were reviewed, first independently and then conjointly. All discrepancies were discussed, specific studies were re-reviewed, and agreement was reached by consensus.

Assessment of study quality
Study quality was assessed, based on previous meta-analytical research, using the following criteria: use of a reliable and valid aggression rating; the presence of a drug-free washout period prior to trial; random assignment of the participants; use of a crossover versus parallel design; and use of double-blinding versus single-blinding. The authors did not specifically state how the papers were assessed for validity. However, it was stated that the studies were reviewed, first independently and then conjointly. All discrepancies were discussed, specific studies were re-reviewed, and agreement was reached by consensus.
Data extraction
The authors did not specifically state how the data were extracted. However it was stated that the studies were reviewed, first independently and then conjointly. All discrepancies were discussed, specific studies were re-reviewed, and agreement was reached by consensus. The categories of data extracted included sample size, primary diagnosis, co-morbid diagnosis, mean age, percentage of males, and drug type, dose and duration.

Methods of synthesis
How were the studies combined?
The effect sizes were estimated using Cohen's d. The 95% confidence intervals (CIs) and weighted mean effect sizes were calculated. To determine the overall significance of the effects, the Stouffer method was used to obtain Z values. Separate analyses were conducted for stimulant effects on overt and covert aggression-related behaviours within the domain of ADHD. The data were analysed separately for the effects on clinician, parent, teacher and overall ratings.

How were differences between studies investigated?
Heterogeneity was investigated using the chi-squared test.

Results of the review
Twenty-eight controlled trials with a total of 683 participants were included.

The mean quality rating was 5.75 (range: 5 to 7) out of a maximum of 7 points.

Overt aggression.

Stimulant treatment significantly improved ratings of aggression.
For clinician ratings (18 independent effect sizes), the combined Z was 6.53 and the weighted mean was 0.769 (95% CI: 0.630, 0.884, p<0.0001). There was significant heterogeneity (p<0.001), suggesting the presence of a one or more mediator variables. The combined Z and weighted mean were 6.09 and 0.710 (95% CI: 0.420, 1.148, p<0.0001), respectively, for parent ratings (13 independent effect sizes), and 8.57 and 1.043 (95% CI: 0.791, 1.323, p<0.0001) for teacher ratings (16 independent effect sizes); the heterogeneity was significant in both cases (p<0.001).

For the overall ratings (28 independent effect sizes), the combined Z was 9.50 and the weighted mean was 0.843 (95% CI: 0.696, 1.024, p<0.0001). There was significant heterogeneity (p<0.001).

Covert aggression.

Stimulant treatment significantly improved ratings of aggression.

For clinician ratings (6 independent effect sizes), the combined Z was 3.35 and the weighted mean was 0.814 (95% CI: 0.199, 1.463, p<0.001). There was significant heterogeneity (p<0.001).

For the overall ratings (7 independent effect sizes), the combined Z was 3.42 and the weighted mean was 0.694 (95% CI: 0.210, 1.292; p<0.001). There was significant heterogeneity (p<0.001).

Authors' conclusions
Stimulant effects for aggression-related behaviours in ADHD have effect sizes similar to those for the core symptoms of ADHD.

CRD commentary
The review question was clearly stated and supported by a priori defined inclusion criteria. It is likely that relevant studies were missed, however, as the studies included in the review were limited to English language studies published in peer-reviewed scientific journals. The data appear to have been pooled appropriately and heterogeneity was assessed.
using a suitable method. The authors referred to the process by which the studies were 'reviewed'. However, it was unclear which aspect(s) of the review process this referred to, i.e. how decisions on the relevance of primary studies were made, how judgements of validity were made, or how the data were extracted. The authors' conclusions appear to follow on from the findings, but they should be viewed in light of the highlighted caveats.

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

**Practice:** The authors state that their findings suggest that, at least in ADHD, pharmacological interventions with stimulants are effective for aggression-related behaviours. In addition, that clinicians might consider pharmacological interventions for overt and covert aggression in ADHD, as well as behavioural treatments.

**Research:** The authors state that given the prevalence and importance of aggressive symptoms influencing clinical referral patterns, symptom severity and outcomes in ADHD children, future clinical drug trials assessing efficacy in ADHD may wish to consider including measures of aggression subtypes in their outcome assessments. In addition, the authors state that their findings support the importance of further psychopharmacological research into the effectiveness of medications for aggression-related behaviours in clinically referred youths.

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