Behavioral and cognitive effects of methylxanthines: a meta-analysis of theophylline and caffeine

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Authors' objectives
To present a meta-analysis of research on the behavioural and cognitive effects of methylxanthines in children.

Searching
MEDLINE, PsycLIT, Dissertation Abstracts and bibliographies from review articles were searched using standard literature search procedures.

Study selection
Study designs of evaluations included in the review
The studies had to include a comparison, i.e. either placebo, alternate drug treatment, baseline or matched control group. Randomisation is not mentioned.

Specific interventions included in the review
Two methylxanthines: theophylline and caffeine.

Participants included in the review
The theophylline meta-analysis included children and adolescents with asthma, whilst the caffeine meta-analysis included normal children and adolescents and those with attention deficit hyperactivity disorder.

Outcomes assessed in the review
The cognitive, behavioural, sleep or psychological effects. The measures from 34 tests and subscales were clustered into 'attention and concentration', 'parent report: internalising', 'parent report: externalising', 'side-effects', 'sleep' and 'teacher reports'.

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 authors performed the selection.

Assessment of study quality
The authors do not report a method for assessing validity.

Data extraction
The authors do not state how the data were extracted for the review, or how many of the authors performed the data extraction.

Methods of synthesis
How were the studies combined?
The effect sizes were calculated. There are no details on the statistical procedures used to combine the studies; however, they were grouped according to psychological tests and questionnaires used.

Mean effect sizes and confidence intervals (CIs) are reported.

How were differences between studies investigated?
The authors do not state how differences between the studies were investigated.
Results of the review

Twelve studies were included in the theophylline meta-analysis (340 children) and 9 studies in the caffeine meta-analysis (193 children).

The results of individual studies are not presented. The mean effect sizes and 95% CIs for the measure clusters in the theophylline meta-analysis are:

- 'attention and concentration', -0.06 (95% CI: -0.17, 0.05);
- 'parent report: externalising', 0.19 (95% CI: -0.09, 0.40);
- 'parent report: internalising', 0.05 (95% CI: -0.13, 0.23);
- 'side-effects', -0.04 (95% CI: -0.30, 0.21);
- 'sleep', -0.04 (95% CI: -0.19, 0.10); and
- 'teacher reports', -0.36 (95% CI: -1.12, 0.32).

None of these reach statistical significance.

The mean effect sizes and 95% CIs for the measure clusters in the caffeine meta-analysis are:

- 'attention and concentration', 0.05 (95% CI: -0.21, 0.32);
- 'parent report: externalising', 1.53 (95% CI: -0.23, 3.30);
- 'parent report: internalising', -0.01 (95% CI: -0.11, 0.09); and
- 'teacher reports', 0.08 (95% CI: -0.01, 0.17).

None of these reach statistical significance. It appears that none of these trials reported outcomes relating to sleep or side-effects.

Authors' conclusions

There is little evidence to suggest that methylxanthines have adverse cognitive or behavioural effects on children. Questions remain with regard to the identification and determinants of either responsive or sensitive subgroups, dose response relationships and the effects of parent-teacher expectancies on behaviour ratings.

CRD commentary

No date parameters, language restrictions or search terms are given so it is not possible to judge how comprehensive the search was.

The authors mentioned that theophylline and caffeine studies vary in quality, but they have not addressed this in the studies included here. There are no details of how data were extracted.

No details of the individual component trials are given.

The combination of the trials is questionable. The study designs varied from before-and-after studies to placebo-controlled trials, and no trial appeared to use randomised allocation to groups. The combination of trials seems to involve using several different measures from the same trial in the clusters; these would not be independent. There are no investigations of the differences between trials.
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