Systematic review of the evidence regarding potential complications of inhaled corticosteroid use in asthma

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CRD summary
This review evaluated the evidence regarding complications of inhaled corticosteroid (ICS) use in people with asthma. The authors concluded that the clinical effectiveness of ICS treatment clearly outweighs the risks. The authors’ conclusions are in line with the evidence they present. However, the validity of the authors' conclusions are limited by selective presentation of only part of the available evidence.

Authors' objectives
To critically evaluate the strength and direction of the available evidence on the complications of inhaled corticosteroid (ICS) use in patients with asthma.

Searching
Randomised controlled trials (RCTs) with less than 15 participants were excluded from the review. RCTs, clinical controlled trials, prospective cohort studies, retrospective cohort studies, cross-sectional observational studies, case series and case-control studies were included in the review. Laboratory studies were also excluded.

Study selection
Study designs of evaluations included in the review
No inclusion criteria regarding the study design were stated.

Specific interventions included in the review
Studies of ICS were eligible for inclusion. Studies looking exclusively at systemic corticosteroids, which focused on asthma disease management or which tested ICS delivery methods, were excluded.

Participants included in the review
Studies of participants (children and adults) with asthma were included in the review. One of the included studies was of participants with chronic obstructive pulmonary disease, and not asthma.

Outcomes assessed in the review
Outcomes relevant to glaucoma, cataracts, skin thinning, ease of bruising, bone density or osteoporosis, or growth retardation as complications of ICS use were included in the review.

How were decisions on the relevance of primary studies made?
A predefined algorithm, in which points were assigned to 20 quality indicators, was used to produce a summary quality score ranging from 0 to 40; specific details were reported. In addition, the strength of evidence supporting each conclusion, based primarily on the robustness of study design and quantity of evidence, was graded from A (best) to D, or F (failed evidence review).

Assessment of study quality
MEDLINE and EMBASE were searched from inception to December 2000; the search terms were not reported. In addition, the references lists of review articles were checked and an expert panel provided any further relevant studies. The studies had to be reported at least partly in English. An expert panel selected studies for the review.

Data extraction
At least two expert panel members independently assessed the quality of the studies.

**Methods of synthesis**

How were the studies combined?
The number of studies and participants included in the review was not reported. One hundred and eight references were included in the review; however, only a summary of the evidence was presented.

How were differences between studies investigated?
The studies were combined in a narrative, grouped by type of adverse event and the review question they were answering. Publication bias was not assessed.

**Results of the review**

At least two expert panel members independently extracted the data from each study into predefined forms. Information on methods for measuring side-effects and for analysis and on study limitations was extracted. A third panel member checked approximately 40% of the studies to ensure the quality of the evidence abstraction.

ICS use is not associated with a reduction in bone density in children (Grade A evidence). Adults with asthma do not usually show a significant reduction in bone mineral density after ICS treatment, although the effect may become clinically important in patients using high-dose ICSs for many years (Grade C evidence).

The risk of subcapsular and nuclear cataracts associated with ICS is negligible in young people with asthma, but may be greater in older people (Grade C evidence). There was insufficient evidence to assess differences in the risk of cataract formation for the different ICS formulations. The dose-effect relationship between ICS use and cataract formation is not well understood (Grade F evidence).

The risk of glaucoma associated with ICS use is probably small, but further study is needed (Grade F evidence). There was insufficient evidence to assess differences in the risk of glaucoma between different ICS formulations (Grade F evidence). There appears to be a poorly studied dose-effect relationship between ICS use and glaucoma (Grade F evidence).

ICS use is associated with a reduction in short-term growth rates in children, but the overall effect is small and may not be sustained with long-term therapy (Grade A evidence). The adult height of asthmatic children treated with ICS is no different from that of non-asthmatic adults (Grade C evidence). There is not enough information about the difference between steroid formulations to draw definitive conclusions regarding their relative effects on growth (Grade C evidence).

ICS use is associated with an increased risk of skin thinning and easy bruising. Dose, duration of use, and gender can affect overall risk (Grade B evidence). There was insufficient information to assess differences in the risk of skin thinning or easy bruising for the different ICS formulations (Grade F evidence). There appears to be a dose-effect relationship between ICS use and skin thinning or easy bruising.

**Authors’ conclusions**

Overall, the evidence suggests that the proven clinical effectiveness of ICS treatment clearly outweighs the proven risks.

**CRD commentary**

The authors set out a clear objective at the beginning of the review, which was supported by clear inclusion criteria for the interventions and broad inclusion criteria for both the participants and outcomes. No inclusion criteria for the study design were stated. Appropriate sources were searched. However, the included studies were limited to those written at least partly in English, which might have introduced language bias, and relevant studies might have been missed. There was little attempt to identify unpublished material and publication bias was not assessed. The data extraction and validity assessment were carried out in duplicate, which helps to reduce the risk of bias, although it was unclear how any disagreements were resolved. Study quality was assessed using appropriate criteria.
Although details of the individual studies were provided, only a summary of selected studies which were thought to 'explain and support the conclusions of the panel' were presented, which may have introduced bias. It was not clear how many and what type of studies were considered for each question. Given the considerable differences between the included studies, the narrative synthesis seemed appropriate. This was a reasonably well-conducted review and the authors' conclusions are in line with the evidence they present. However, the validity of the authors' conclusions is limited by the selective presentation of only part of the available evidence.

**Implications of the review for practice and research**
The authors did not state any implications for practice or further research.

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