CRD summary
The review assessed the effects of inhaled budesonide on the risk of pneumonia in patients with chronic obstructive pulmonary disorder. The authors concluded that budesonide treatment did not increase the risk of pneumonia and was safe. The small number of events in the analyses, coupled with limitations in review methodology, means the authors' conclusions should be interpreted with caution.

Authors' objectives
To assess the effects of inhaled budesonide on the risk of pneumonia in patients with chronic obstructive pulmonary disorder.

Searching
MEDLINE, EMBASE and an internal AstraZeneca database (Planet) were searched with no language or date restrictions. Search terms were reported.

Study selection
Double-blinded randomised controlled trials (RCTs) of at least six months' duration, comparing budesonide or budesonide and formoterol with placebo or formoterol alone, in patients with chronic obstructive pulmonary disorder, were eligible for inclusion. Chronic obstructive pulmonary disorder had to be defined either by clinical diagnosis or as current or former smoker (10 pack-year smoking history or over) with a forced expiratory volume (in one second) \( (FEV_1) \) to forced vital capacity ratio of less than 0.7. Trials of patients with asthma or with evidence of reversibility by standard bronchodilator testing were excluded.

The mean age of included participants was 61.6 years, with 70% being male, and 51% being smokers at enrolment. Participants in all trials were stable at the time of enrolment. Budesonide doses were most commonly 640 μg daily, but ranged from 320 to 1280 μg daily. The primary outcome of the review was patient-reported pneumonia as an adverse event or serious adverse event.

Two reviewers independently selected studies for inclusion

Assessment of study quality
The authors assessed study quality using the Jadad scale (trials were scored out of 5 points).

The authors did not state how many reviewers performed the assessment.

Data extraction
Intention-to-treat data were extracted and hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated.

The authors did not state how data were extracted for the review, or how many reviewers performed the data extraction.

Methods of synthesis
Meta-analyses of pooled hazard ratios were performed; the model used was not stated. Pooled Kaplan-Meier curves were generated using a log-rank statistic to calculate differences between curves. Cox proportional hazards regression was used to adjust for potential confounding variables. Exploration of heterogeneity was limited to a \( \chi^2 \) test comparing the difference in reporting of adverse events and serious adverse events between countries.

Results of the review
Seven trials were included in the review (n=7,042 participants). Sample sizes ranged from 75 to 1,964 participants. All
trials were reported as being of high quality (Jadad score of 4 and over).

There were no significant differences between treatment groups for: pneumonia occurring as an adverse event (HR 1.05, 95% CI: 0.81 to 1.37) or as a serious adverse event (HR 0.92, 95% CI: 0.62 to 1.35); or for time to pneumonia occurring as an adverse event or serious adverse event. Increasing age and decreasing percent of predicted forced expiratory volume (FEV₁) were the only two variables significantly associated with occurrence of pneumonia as an adverse event or serious adverse event.

Authors' conclusions
Budesonide treatment for 12 months did not increase the risk of pneumonia in patients with chronic obstructive pulmonary disorder during that time and therefore is safe for clinical use in such patients.

CRD commentary
The review addressed a clear question, supported by appropriate inclusion criteria. However, it was unclear why a trial which failed one of the criteria was still included in the review. A search to identify studies in any language was conducted using electronic databases. Although the authors reported use of the Jadad scale to assess study quality, this appears not to be a very informative assessment for a review restricted to including only double-blinded, randomised trials. Two reviewers independently selected trials for inclusion, but details of the processes used for quality assessment and data extraction were not reported; this possibly subjected the review to risk of reviewer error and bias. Despite thorough details being provided for most aspects of the included trials, it was still unclear which comparator treatments were used (placebo or formoterol), making it difficult to interpret individual trial results. Appropriate methods appeared to be used to pool data, although the authors did not state whether they used a fixed-effect or random-effects model. Statistical heterogeneity between trials was not formally assessed. The authors noted that none of the trials were powered specifically to detect pneumonia (out of the 14 treatment arms, only three reported occurrence of more than 20 adverse events). It appears likely that the trials were too small to reliably address the authors’ objectives. In light of this, and other limitations of the review, the authors’ conclusions should be interpreted with caution.

Implications of the review for practice and research
Practice: The authors stated that budesonide treatment for 12 months does not increase the risk of pneumonia in patients with chronic obstructive pulmonary disorder who use inhaled corticosteroids and is safe for clinical use in such patients.

Research: The authors stated that future research should clarify the mechanisms by which inhaled corticosteroids contribute to pneumonia, and how the risk is modified by differences in dosing and pharmacokinetics. They also stated that in future studies of chronic obstructive pulmonary disorder, local language and other regional factors should be considered in the reporting of pneumonia as an adverse event or serious adverse event.

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.