The transitivity assumption

The Airways Group has recently published its first network meta-analysis (NMA) (Kew 2014) and there is a growing interest in these kinds of reviews. NMA is a statistical tool used to rank three or more different treatments for a particular condition such as COPD. However, we need to be mindful about whether the different trials in the analysis are similar enough to make any comparisons worthwhile. Are the treatments similar enough? Do they reflect real treatment decisions? Are the participants comparable and at the same stage in their disease? This is called the transitivity assumption. Here, Chris Cates explains transitivity from the point of view of multi-arm RCT, before explaining how the transitivity assumption applies in a NMA.

Chris Cates, Co-ordinating Editor

GRADE and common errors

Toby Lasserson, formerly from the CAG and now Senior Editor at the Cochrane Editorial Unit, has recently produced two documents. The first provides some common errors and examples of good practice in Cochrane Reviews and the second on how to incorporate the GRADEing of the evidence throughout the review. There are plenty of examples there to have a look at.

Emma Welsh, Managing Editor

Programme grant news

In February, after months of hard work and trepidation, we received the email we’d been hoping for – we were successful in our bid for a Cochrane programme grant!

The programme of work was carefully compiled to cover areas of asthma therapies and management that are of particular relevance to the National Health Service (NHS) in the UK, but the majority are just as important further afield. Our existing Systematic Reviewer, Kayleigh, will be working on the reviews with researchers and clinicians, particularly through the Lancashire and Cumbria Clinical Research Hub, with whom we planned the proposal.

May and June saw Kayleigh and Becky begin work on three programme grant protocols covering the first theme of the grant, asthma therapies. These are currently at peer review stage.

In September, we will be running a priority-setting workshop with the Lancaster Hub, representatives from Asthma UK, and consumers. The aim is to identify research questions relating to asthma self-care which are important to people affected by asthma. We will also be looking at what outcomes are most important to people in the workshop - as we are part of the ‘Outcomes Most Important to Patients, Public and Practitioners’ being run by the UK Cochrane Centre. The key themes are to refine questions within the second theme of the grant, asthma management, with topics such as assessment of asthma control, adherence, and care pathways. Keep an eye out for our next newsletter to hear how we get on.

Kayleigh Kew, Systematic Reviewer
PRISMA Study flow diagrams in review updates

The Cochrane MECIR standards ask for a PRISMA diagram in all new Cochrane reviews and there is clear guidance on how to do this in the PRISMA statement. But when it comes to updating your review, how should you complete one of these diagrams? Some of my TSC colleagues from other Cochrane groups and I discussed this subject and presented an adapted diagram in this recently published open access paper. In case you haven’t got time to read the paper now, I’ve reproduced the PRISMA diagram here:

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Liz Stovold, Trials Search Co-ordinator
Clinical guidelines

Cochrane reviews and clinical guidelines are closely interlinked. Airways reviews underpin several international guidelines. As of April 2014, we have 157 reviews in 16 guidelines (6 UK, 4 American, 3 Australian, and 3 Canadian). 69 reviews have been used in more than one guideline (44 in 2; 19 in 3; 6 in 4). Airways also has the highest number of Cochrane reviews in any one guideline (n=76) in the Australian national asthma guidelines (Data kindly provided by the UK Cochrane Centre Guidelines Project).

Increasingly, we try to accommodate the needs of guideline writers beyond writing and publishing reviews. Authors have helped with tasks such as performing additional subgroup analyses, sending extracted data to guideline writers before completion of the initial review draft, provided additional literature searches, assisted with screening searches and attended guideline meetings to provide evidence to proceedings. We also use links with guideline writing teams to identify important new reviews and updates and provide them in a timely fashion.

Guideline teams have also contributed to updating reviews which were needed for their guidelines for example 'Hospital at home for acute exacerbations of chronic obstructive pulmonary disease’ (Jeppesen 2012).

Cochrane Airways is now curating a collection of clinical guidelines on Zotero which we hope will be a useful resource for authors and clinicians. If you know of any guidelines or consensus statements that are not included or which have been updated, please contact ewelsh@sgul.ac.uk sending me the link to where it is published.

The Embase screening project

The CENTRAL database of trials on the Cochrane Library contains reports identified from multiple databases. One of these databases, Embase, is being screened by the ‘crowd’ in an innovative new project. Anyone can sign up to help screen the literature for CENTRAL. It is a good way for students to learn about clinical trial designs or a gentle entry point for people new to Cochrane to get involved. If you or anyone you know is interested in joining the crowd, you can find more details here:

Liz Stovold, Trials Search Co-ordinator
Airways reviews in the news!

As anticipated *Inhaled corticosteroids in children with persistent asthma: effects on growth* (Zhang 2014) was widely covered by the media a few weeks ago, with most news sources responsibly including warnings from independent researchers and doctors that uncontrolled asthma can be dangerous.

The *Independent* correctly reported that the effect of inhalers on growth was “a small price to pay” to protect against potentially lethal asthma attacks.

Liz Stovold – elected to Steering Group

The Airways Group is delighted to announce that following elections in July, Liz was formally announced as the TSC representative on the Cochrane Collaboration Steering Group (CCSG). The Steering Group has overall responsibility for overseeing the development and implementation of policy affecting The Cochrane Collaboration. The Steering Group also has legal responsibility as the Board of Directors for The Cochrane Collaboration as a registered charity. Liz officially takes up her new position at the 2014 Cochrane Colloquium in Hyderabad, India.

@CochraneAirways

You don’t even need a Twitter account to see what the Airways Group is tweeting these days! Just follow us via our Twitter feed on our [website](#).

Hi to...Becky Normansell (again!)

Since our [last newsletter](#) we are very pleased and proud to announce that as of 1 June 2014, Becky Normansell became our Deputy Co-ordinating Editor on a part-time basis alongside Chris. She continues to work part-time as a GP in South London.

This year’s Cochrane Colloquium will focus on ‘Evidence-Informed Public Health: Opportunities and Challenges’. Liz, Kayleigh and Becky will be there – come and say hello if you plan to attend.

*Emma Jackson, Editorial Assistant*
New reviews March 2014-present
Bronchial thermoplasty for moderate or severe persistent asthma in adults, Torrego A, Solà I, Munoz AM, Roqué i Figuls M, Yepes-Nuñez JJ, Alonso-Coello P, Plaza V

Background
Asthma is a chronic condition in which people experience symptoms of breathlessness, wheezing, coughing and chest tightness due to airway inflammation and airway muscle contraction. With inhaled treatments, including bronchodilators (drugs that relax airway muscle and so open up the airways) and steroids (which treat underlying inflammation in the lungs), symptoms usually can be controlled. However, for some people, asthma cannot be adequately controlled with these drugs, either because they are truly resistant or because they do not take them.

The muscle in the airways of the lungs is thicker in people with asthma than in people who do not have asthma. During asthma attacks, these muscles tighten, making it hard to breathe.

Bronchial thermoplasty is a relatively new procedure that reduces the amount of muscle bulk in the airways of the lungs. A long flexible tube, called a bronchoscope, is passed down into the lung under direct observation, and the walls of specific areas of the lungs are heated to 65 degrees Celsius. This causes some of the muscle to break up, making it harder for the muscles to tighten.

Generally, three sessions of treatment are given.

Review question
We reviewed the effects of bronchial thermoplasty in people with asthma.

Study characteristics
We found three trials comparing groups of adults treated with bronchial thermoplasty versus adults who received standard medical treatment or a "sham" (simulated) bronchial thermoplasty treatment.

Key results
These studies showed moderate improvement only in quality of life of patients treated with bronchial thermoplasty and in the number of asthma attacks (exacerbations) that they experienced. In addition, patients treated with this procedure had more respiratory problems than patients who received the alternative intervention during the period when they were undergoing treatment, resulting in increased risk of hospitalisation due to a respiratory symptom during this phase, but not afterward.

Quality of evidence
Confidence in the results of this review is moderate because two of the studies had no sham intervention and there were differences regarding the characteristics of patients and the comparisons performed. More studies should be conducted to determine whether the observed effect and safety of bronchial thermoplasty are durable over the long term, and to identify whether particular patients can be identified who could benefit most.

This plain language summary is current as of January 2014.

Inhaled steroids and risk of pneumonia for chronic obstructive pulmonary disease, Kew KM, Seniukovich A

Why is this question important?
Inhaled corticosteroids (ICS) are drugs that can reduce the occurrence of COPD flare-ups and improve quality of life. In COPD, ICS are commonly used alongside long-acting beta2-agonists (LABA). The most common combinations of ICS and LABA inhalers are fluticasone and salmeterol, and budesonide and formoterol, but fluticasone furoate is also used once daily with a new LABA called vilanterol. Lots of studies have shown benefits of ICS, but they can also increase the risk
of pneumonia. Added to this concern, pneumonia can be difficult to diagnose, and the severity of pneumonia can be poorly reported in trials. Therefore even though we have reviews on inhaled steroids for COPD, we wanted to do a review exclusively on pneumonia, so we could take a closer look at the evidence.

The overall aim of this review is to assess the risk of pneumonia for people with COPD taking fluticasone or budesonide.

**How did we answer the question?**
We looked for all studies comparing budesonide or fluticasone versus a dummy inhaler (placebo), and all studies comparing their use in combination with a LABA (i.e. budesonide/formoterol, fluticasone propionate/salmeterol, and fluticasone furoate/vilanterol) versus the same dose of LABA alone. This allowed us to assess the risk of ICS used alone or in combination with LABA.

**What did we find?**
We found 43 studies including more than 30,000 people with COPD. More studies used fluticasone (26 studies; 21,247 people) than budesonide (17 studies; 10,150 people). A higher proportion of people in the studies were male (around 70%), and their COPD was generally classed as severe. The last search for studies to include in the review was done in September 2013.

We compared each drug against controls and assessed separately the results of studies that compared ICS versus placebo, and an ICS/LABA combination versus LABA alone. We also conducted an indirect comparison of budesonide and fluticasone based on their effects against placebo, to explore whether one drug was safer than the other.

Fluticasone increased ‘serious’ pneumonias (requiring hospital admission). Over 18 months, 18 more people of every 1000 treated with fluticasone were admitted to hospital for pneumonia.

Budesonide also increased pneumonias that were classed as ‘serious’. Over nine months, six more hospital admissions were reported for every 1000 individuals treated with budesonide. A lower dose of budesonide (320 mcg) was associated with fewer serious pneumonias than a higher dose (640 mcg).

No more deaths overall were reported in the ICS groups compared with controls, and deaths related to pneumonia were too rare to tell either way.

When we compared fluticasone and budesonide versus each other, the difference between them was not clear enough to tell whether one was safer (for pneumonia, requiring a hospital stay, general adverse events and death). The risk of any pneumonia event (i.e. less serious cases that could be treated without going to hospital) was higher with fluticasone than with budesonide.

Evidence was rated to be of high or moderate quality for most outcomes. When an outcome is rated of high quality, further research is very unlikely to change our confidence in the estimate of effect, but moderate ratings reflect some uncertainty in the findings. Results from the budesonide studies were generally less clear because they were based on fewer people, and the studies were shorter.

**Conclusion**
Budesonide and fluticasone, delivered alone or in combination with LABA, can increase serious pneumonias that result in hospitalisation of people. Neither has been shown to affect the chance of dying compared with not taking ICS. Comparison of the two drugs revealed no difference in serious pneumonias or risk of death. Fluticasone was associated with a higher risk of any pneumonia (i.e. cases that could be treated in hospitalisation).
the community) than budesonide, but potential differences in the definition used by the respective drug manufacturers reduced our confidence in this finding. These concerns need to be balanced with the known benefits of ICS (e.g. fewer exacerbations, improved lung function and quality of life).

Researchers should remain aware of the risks associated with ICS and should make sure that pneumonia is properly diagnosed in studies.

Long-acting inhaled therapy (beta-agonists, anticholinergics and steroids) for COPD: a network meta-analysis, Kew KM, Dias S, Cates CJ

Why is this question important?
Inhaled drugs for COPD have been shown to relieve symptoms, improve quality of life and prevent or treat flare-ups. Treatment with these inhaled drugs tends to begin with one inhaler, and additional therapies are introduced as necessary. For persistent or worsening symptoms, long-acting inhaled drugs taken once or twice daily are preferred over short-acting ones. Several Cochrane reviews have looked at the risks and benefits of specific long-acting inhaled therapies compared with placebo or other treatments. However for patients and clinicians, it is important to understand the benefits of these treatments relative to each other, and whether a particular type of inhaled therapy is more beneficial than the others.

How did we answer the question?
We looked for studies in existing Cochrane reviews and performed detailed electronic searches up to September 2013. Studies were included if they lasted at least six months and compared any of the following treatments versus any other for people with COPD: long-acting beta2-agonists (LABAs—formoterol, indacaterol, salmeterol); long-acting muscarinic antagonists (LAMAs—aclidinium, glycopyrronium, tiotropium); inhaled corticosteroids (ICSs—budesonide, fluticasone, mometasone); combination long-acting beta2-agonist and inhaled corticosteroid (LABA/ICS—formoterol/budesonide, formoterol/mometasone, salmeterol/fluticasone); and placebo.

We conducted a network meta-analysis to assess the benefits of each type of treatment (e.g. long-acting beta2-agonists) relative to the others for quality of life and lung function. We also looked at how much individual treatments varied (e.g. How different were the three inhaled steroids from one other?) and whether particular treatments were more effective than others. We assessed the data for six months and 12 months separately and reported six months as the primary findings.

What did we find?
We found 71 relevant studies, but not all measured the outcomes we were interested in. Forty-two studies were included in the quality of life analyses (measured on St George’s Respiratory Questionnaire), and 46 were included in the lung function analyses.

Evidence from good quality and similar trials supported LABA/ICS combinations as the most likely treatment strategy to bring the greatest improvement to quality of life and lung function. Combination therapy gave an average benefit of 3.9 units over placebo at six months. LAMAs and LABAs were ranked second and third at six months (-2.63 and -2.29 units, respectively), especially when unreliable trials were not included, but a large degree of overlap in the estimates was noted.

Combination LABA/ICS was the highest ranked class for trough forced expiratory volume in one second (FEV1), with mean improvement over placebo of 133 mL at six months (95% credible Interval (CrI) 101 to 164). As was the case for SGRQ, LAMAs (mean difference (MD) 104, 95% CrI 82 to 125) were ranked just ahead of LABAs (MD 99, 95% CrI 72 to 128) at six months, and ICSs
were the lowest ranked class (MD 65, 95% CrI 33 to 97).

For both outcomes, the effects of LABA and ICS used alone appeared to increase when used together for six months, but initial differences between the treatment classes were less obvious after a year of treatment.

Conclusion
Quality of life and lung function were improved most on combination inhalers (LABA and ICS) and least on ICS alone at 6 and 12 months. Overall LAMA and LABA inhalers had similar effects, particularly at 12 months. The network has demonstrated the benefit of ICS when added to LABA for these outcomes in participants who largely had an FEV1 that was less than 50% predicted, but the additional expense of combination inhalers and any potential for increased adverse events (which has been shown by other reviews) require consideration. Our findings are in keeping with current National Institute for Health and Care Excellence (NICE) guidelines.

Intravenous magnesium sulfate for treating adults with acute asthma in the emergency department, Kew KM, Kirtchuk L, Michell CI

Why is this question important?
Asthma is a long-term condition that causes coughing, wheezing, shortness of breath and chest tightness. When symptoms significantly worsen, often referred to as an attack or 'exacerbation,' this can be life threatening. Management of exacerbations in the emergency department (ED) varies, and some guidelines recommend the use of intravenous magnesium sulfate (IV MgSO4) when other treatments have not helped. However, it is unclear whether IV MgSO4 is effective, particularly in less severe cases, and we wanted to answer this question.

How did we answer the question?
We looked for trials that compared IV MgSO4 versus placebo in adults attending the ED with an asthma exacerbation. The most recent searches were done on 2 May 2014. We were interested primarily in whether IV MgSO4 reduced the number of people needing to be admitted to hospital, and we looked at several other measures as well, including time spent in the ED, lung function and symptom scores.

What did we find?
Fourteen studies met the inclusion criteria, involving a total of 2313 people. These studies varied in terms of how bad exacerbations had to be for people to be included and in terms of what other treatments were provided before IV MgSO4 was given, but almost all trials gave participants at least oxygen, nebulised short-acting medications and steroid tablets or injection.

Overall, IV MgSO4 reduced the need for hospital admission compared with placebo (seven fewer per 100 treated; 95% confidence interval two to 13 fewer). Not enough information was available to show whether the reduction in hospital admissions was associated with severity of the asthma exacerbation, or whether it made a difference what other treatments were given. Evidence suggests that IV MgSO4 improved some lung function parameters, but for other measures such as heart rate, variation among study findings reduced our confidence in the results. We did not find a difference between IV MgSO4 and placebo in most other measures (including time spent in the ED, respiratory rate and blood pressure), and adverse events generally were poorly reported.

Conclusion
This review showed that IV MgSO4 reduces hospital admissions and improves lung function in adults with exacerbations of asthma when other first-line medications have not relieved the acute symptoms (i.e. oxygen, inhaled short-acting...
medications and IV steroids). Evidence for other measures of benefit and safety was limited.

Researchers should clearly define the severity of the asthma condition among people in their studies while carefully recording adverse events.

This plain language summary is current as of May 2014.

Non-invasive ventilation during exercise training for people with chronic obstructive pulmonary disease, Menadue C, Piper AJ, van ’t Hul AJ, Wong KK

Background
Quality of life and exercise tolerance are commonly reduced in people with chronic obstructive pulmonary disease (COPD). In addition, physical activity levels are lower compared with those of healthy people of a similar age. Exercise training as a part of a formal rehabilitation programme is an important component of management for people with COPD and has been shown to improve both quality of life and exercise tolerance. However, some individuals may have difficulty performing exercise at an adequate training intensity. Non-invasive ventilation (NIV) is a method of providing breathing support using a machine called a ventilator. Breathing support is delivered via a mask that is worn over the nose, mouth or both, or via a mouthpiece. During a single exercise session, NIV has been shown to improve exercise tolerance and reduce breathlessness. Consequently, NIV used over multiple exercise sessions (during exercise training) may allow people with COPD to exercise at a higher intensity and potentially to achieve greater improvement in exercise tolerance, quality of life and physical activity.

Review question
We conducted a review to determine whether NIV during exercise training affects exercise tolerance, quality of life and physical activity compared with exercise training alone or exercise training with sham NIV (placebo) in people with COPD.

Study characteristics
The evidence is current to November 2013. We included six studies involving 126 participants who completed the study protocols. Most studies recruited participants with severe to very severe COPD. The average age of participants ranged from 63 to 71 years. Cycling or treadmill exercise training was performed in the studies. The duration of exercise training programmes ranged from six to twelve weeks.

Key results
The percentage change in peak exercise capacity increased by an average of 17% in three studies, and the percentage change in endurance exercise capacity by an average of 59% in two studies that provided NIV during training compared with training without NIV or training with sham NIV. However, these improvements in exercise capacity were not consistent findings as there was no clear evidence that NIV improved all other measures of exercise capacity. The results for quality of life were uncertain and our analysis did not exclude there being an effect with NIV during exercise training in two studies. Physical activity was not assessed in any of the studies. Non-invasive ventilation allowed participants to exercise at a higher training intensity (average of 13% higher) in three studies, and evidence of a greater training effect on the muscles was found in two studies, as a marker in the blood (isoload blood lactate) was significantly lower by an average of 0.97 mmol/L. No information regarding adverse events or cost was reported. It is currently unknown whether demonstrated benefits of NIV during exercise training are clinically worthwhile or cost-effective.
Quality of the evidence
This review was generally limited by the small number of included studies and the small numbers of participants within the included studies. The quality of the evidence was low for exercise capacity outcomes, largely because of issues with study design. Consequently, the effect of NIV during exercise training on exercise capacity is uncertain. The quality of the evidence for quality of life, training intensity and isoload blood lactate was moderate, and these findings can be interpreted with a greater degree of confidence.


Background
Stress may cause worsening of asthma. Previous studies showed that "written emotional disclosure," an activity that encourages people to write about stressful experiences, helps to reduce stress and improve well-being. Therefore written emotional disclosure may have a role in the management of asthma by reducing stress.

Review question
We reviewed the medical literature to find out whether written emotional disclosure improves lung function and asthma symptoms in asthmatic patients. We looked at studies that compared the effectiveness of completing written emotional disclosure versus writing about topics unrelated to emotion.

Study characteristics
Four studies, involving 414 participants, were included in this review. The trials lasted between two months and 12 months. One study was conducted in the UK, the other three in the USA. All studies compared emotional disclosure writing versus non-stressful writing. Three studies were conducted in adult participants and one in adolescents. The average age of participants ranged from 14 to 43 years. In all trials, most of the participants were female.

Key results
There is no evidence to support that written emotional disclosure is helpful in improving lung function or symptoms in patients with asthma. However, disclosure may be beneficial for patients' perceptions of their own asthma control. Based on evidence obtained from the studies, we are not able to draw conclusions about the role of written emotional disclosure in quality of life, psychological well-being, asthma medication use or use of healthcare facilities for asthma-related problems. Better designed studies are necessary to determine the effects of written emotional disclosure for patients with asthma.

Quality of the evidence
Our interpretation of the studies was limited by variation in study settings, topics of the non-stressful writing exercise and study duration. The evidence presented in this review is generally of low quality. This summary was current to January 2014.

Anticoagulation therapy versus placebo for pulmonary hypertension, Ezedunukwe IR, Enuh H, Nfonoyim J, Enuh CU

Background
The heart has four chambers: two upper and two lower chambers. The lower right chamber, also known as the right ventricle, pumps blood through the pulmonary artery to the lungs, where the blood receives oxygen. Pulmonary hypertension occurs when pressure in the pulmonary arteries is increased to above normal (8 to 25 mmHg). When this happens over time, inflammation of the pulmonary artery occurs. The arteries may then become stiff and tighten. These changes make it difficult for the heart to pump blood to the lungs. The heart becomes weaker as it tries to push against this pressure; the resulting disturbance to blood flow can lead to blood clots.
These clots can travel to the lungs, which can worsen the person’s condition and may result in death.

People with pulmonary hypertension may complain of tiredness, chest pain and shortness of breath during normal activities like walking and running, which may progress to affect all physical activities. Prospects of survival depend on several factors, but pregnancy is strongly associated with poor survival.

Treatment of this disease is multi-faceted and includes rehabilitation, psychosocial support and surgical and medical treatment. Medical treatment includes the use of blood thinners such as warfarin, heparin, fondaparinux, argatroban, dabigatran, apixaban and rivaroxaban. Blood thinners work by preventing the formation of clot. The blood thinner of choice, warfarin, needs close monitoring with daily to weekly laboratory testing to maintain the therapeutic target; this monitoring may be difficult to keep up with. The major side effect of blood thinners is bleeding, which can manifest as easy bruising, bleeding in the digestive tract and bleeding into the brain; severe cases can be fatal.

**Review question**

We set out to evaluate the effectiveness of blood thinners in the treatment of pulmonary hypertension. No eligible studies (randomised controlled trials) were found. Review of other studies (non-randomised controlled trials) shows the effectiveness of this intervention. However, these findings should be interpreted with caution. We are uncertain as to how far the results of studies with this design can be believed, and our own approach was not designed to properly look for them and incorporate them in our systematic review. This review therefore highlights the need for appropriately designed randomised controlled trials.

**Combination inhaled corticosteroids and long-acting beta2-agonists for children and adults with bronchiectasis, Goyal V, Chang AB**

A paucity of evidence is available to allow conclusions on whether combined inhaled corticosteroids (ICS)-long-acting beta2-agonists (LABA) are equivalent or superior to placebo or ICS monotherapy for the treatment of stable or exacerbation (flare-up) state bronchiectasis (Appendix 2).

**Review question**

Is any evidence available to show that combined ICS-LABA is superior to placebo or ICS monotherapy for the treatment of stable or exacerbation state bronchiectasis in children and adults?

**Study characteristics**

A small, single-centre, non-blinded study that compared inhaled ICS-LABA with high-dose ICS.

**Key results**

A single study showed some benefit of the inhaled ICS-LABA combination over high-dose ICS in terms of indices of clinical stability such as dyspnoea (shortness of breath), cough-free days and number of exacerbations but failed to show significant improvement in lung function or microbiology. No data are available on children with bronchiectasis or adults with bronchiectasis during an exacerbation phase. Until further evidence becomes available, we recommend that use of combined ICS-LABA should be individualised according to the presence or...
likelihood of co-existing asthma features and risks of medications.

Quality of the evidence
This review is based on a single study, hence the quality of evidence is substantially limited.

Bottom line
The decision to use combined ICS-LABA in bronchiectasis must be made for individual patients on the basis of the presence or absence of bronchial hyperreactivity, until further randomised controlled trials are conducted to answer this important question.

Vitamins C and E for asthma and exercise-induced bronchoconstriction, Wilkinson M, Hart A, Milan SJ, Sugumar K

Review question
We considered in this review whether vitamins C and E, when taken together daily, may be helpful for people with asthma or exercise-induced breathlessness.

Background
Asthma is an inflammatory lung condition characterised by narrowing of the airways; it is associated with breathlessness, chest tightness, cough and wheezing. The condition affects quality of life. It is estimated that more than 300 million people suffer from asthma, and vitamins C and E have been suggested as supplements that might help to reduce symptoms.

Study characteristics
Five studies comparing vitamins C and E versus placebo (no vitamins C and E) in 214 people with asthma or exercise-induced breathlessness were included in this review. Four studies included adults, and one included children. The very limited number of studies available for review and their different designs meant that we were only able to describe individual studies, rather than pooling their results to determine an average result. In most study reports, the design was not well described; therefore it was impossible to assess the risk of bias for most of the studies. In terms of our key outcomes, very few relevant data were provided by the trial authors.

Key results
We found no indication of benefit in the studies that considered vitamins C and E in relation to asthma. However, at this stage, it is not possible to form any clear conclusions based on these findings, as available evidence is insufficient to allow proper assessment of the use of vitamins C and E as treatment for patients with asthma. Additional well-designed research is required to answer this question.

Quality of the evidence
How patients were allocated to receive either vitamins C and E or placebo was not clearly described in any of the five included studies. This may mean that the studies were not well randomised, which can affect the results. A second concern is that the designs of the studies were different, which means that we cannot be certain that the studies were measuring the same thing. By taking this into account, we judged the evidence in this review overall to be of low to moderate quality.

Inhaled anticholinergics and short-acting beta2-agonists versus short-acting beta2-agonists alone for children with acute asthma in hospital, Vézina K, Chauhan BF, Ducharme FM

Background
Anticholinergics (e.g. ipratropium bromide, atropine sulfate) are inhaled drugs. They relax the airway muscles and decrease secretions. Anticholinergics are sometimes used in addition to beta2-agonists (such as salbutamol and terbutaline), which are potent drugs given to relax smooth muscles in the airways in children with acute asthma. We do not know whether the addition of inhaled anticholinergics to beta2-
agonists is beneficial for children hospitalised with acute asthma.

**Review question**

We wished to examine the efficacy and safety of inhaled or nebulised (mist inhaled into the lungs) anticholinergics added to beta2-agonists compared with beta2-agonists alone in children one to 18 years of age hospitalised for an acute asthma exacerbation.

**Study characteristics**

In reviewing evidence available until November 2013, we found seven eligible studies of children hospitalised with acute asthma; four of these studies (472 children one to 18 years of age) contributed data to the review. Four studies compared the combination of anticholinergics (ipratropium bromide) and beta2-agonists versus the same dose of beta2-agonists alone. Included studies enrolled both girls and boys, with a gender ratio ranging from 59% to 73% males.

**Results**

No additional benefit was noted by adding anticholinergics to β2-agonists in terms of duration of hospital stay in patients compared to those who received beta2-agonists alone. Two of four trials (50%) contributing data were deemed of high methodological quality. No trial reported information on serious adverse events. No statistically significant group difference was noted in other markers of response to therapy, that is, the need for supplemental asthma therapy, time to short-acting beta2-agonists spaced at four hours or longer, asthma clinical scores, lung function and overall withdrawals for any reason.

**Conclusion:** No apparent benefit is derived from adding anticholinergics to beta2-agonists in children hospitalised for an acute asthma exacerbation, that is, beyond initial treatment in the emergency department. No adverse health effects were reported, yet the small number of trials combined with inadequate reporting prevents firm reassurance regarding the safety of anticholinergics. In the absence of trials conducted in the intensive care unit (ICU), no conclusion can be drawn regarding children with very severe exacerbations who are admitted to the ICU. Our findings support the ongoing recommendations provided by national and international guidelines.

**Quality of the results**

This review is based on a small number of identified trials conducted in children with acute asthma. All trials contributing to the primary outcome are of high methodological quality, but they are few. As the addition of new trials may change the conclusion, the quality of evidence was downgraded from high to moderate. Additional and larger trials are needed.

**Inhaled corticosteroids in children with persistent asthma: dose-response effects on growth**, Pruteanu AI, Chauhan BF, Zhang L, Prietsch SOM, Ducharme FM

**Background**

Asthma guidelines recommend inhaled corticosteroids (ICS) as the first choice of treatment for children with persistent asthma that is not well controlled when only a reliever inhaler is used to treat symptoms. Steroids work by reducing inflammation in the lungs and are known to control underlying symptoms of asthma. However, parents and physicians remain concerned about the potential negative effect of ICS on growth.

**Review question**

Does altering the dose of inhaled corticosteroids make a difference in the growth of children with asthma?

**What evidence did we find?**

We studied whether a difference could be seen in the growth of children with persistent asthma who were using different doses of the same ICS
molecule and the same delivery device. We found 22 eligible trials, but only 10 of them measured growth or other measures of interest. Overall, 3394 children included in the review combined 17 group comparisons (i.e. 17 groups of children with mild to moderate asthma using a particular dose and type of steroid in 10 trials). Trials used different ICS molecules (beclomethasone, budesonide, ciclesonide, fluticasone or mometasone) either on their own or in combination with a long-acting beta2-agonist (a drug used to open up the airways) and generally compared low doses of corticosteroids (50 to 100 μg) with low to medium (200 μg) doses of corticosteroids (converted in μg HFA-beclomethasone equivalent) over 12 to 52 weeks.

Results
We found a small but statistically significant group difference in growth over 12 months between these different doses clearly favouring the lower dose of ICS. The type of corticosteroid among newer molecules (ciclesonide, fluticasone, mometasone) did not seem to influence the impact on growth over one year. Differences in corticosteroid doses did not seem to affect the change in height, the gain in weight, the gain in bone mass index and the maturation of bones.

Quality of the evidence
This review is based on a small number of trials that reported data and were conducted on children with mild to moderate asthma. Only 10 of 22 studies measured the few outcomes of interest for this review, and only four comparisons reported growth over 12 months. Our confidence in the quality of evidence is high for this outcome, however it is low to moderate for several other outcomes, depending on the number of trials reporting these outcomes. Moreover, a few outcomes were reported only by a single trial; as these findings have not been confirmed by other trials, we downgraded the evidence for these outcomes to low quality. An insufficient number of trials have compared the effect of a larger difference in dose, for example, between a high dose and a low dose of ICS and of other popular molecules such as budesonide and beclomethasone over a year or longer of treatment.

Conclusions
We report an evidence-based ICS dose–dependent reduction in growth velocity in prepubescent school-aged children with mild to moderate persistent asthma. The choice of ICS molecule (mometasone, ciclesonide or fluticasone) was not found to affect the level of growth velocity response over a year. The effect of corticosteroids on growth was not consistently reported: among 22 eligible trials, only four comparisons reported the effects of corticosteroids on growth over one year. In view of parents' and clinicians' concerns, lack of or incomplete reporting of growth is a matter of concern given the importance of the topic. We recommend that growth be systematically reported in all trials involving children taking ICS for three months or longer. Until further data comparing low versus high ICS dose and trials of longer duration are available, we recommend that the minimal effective ICS dose be used in all children with asthma.

Inhaled corticosteroids in children with persistent asthma: effects on growth, Zhang L, Prietsch SOM, Ducharme FM

Review question
We reviewed the evidence on whether inhaled corticosteroids (ICS) could affect growth in children with persistent asthma, that is, a more severe asthma that requires regular use of medications for control of symptoms.

Background
Treatment guidelines for asthma recommend ICS as first-line therapy for children with persistent asthma. Although ICS treatment is generally considered safe in children, parents and
physicians always remain concerned about the potential negative effect of ICS on growth.

Search date
We searched trials published until January 2014.

Study characteristics
We included in this review trials comparing daily use of corticosteroids, delivered by any type of inhalation device for at least three months, versus placebo or non-steroidal drugs in children up to 18 years of age with persistent asthma.

Key results
Twenty-five trials involving 8471 children with mild to moderate persistent asthma (5128 treated with ICS and 3343 treated with placebo or non-steroidal drugs) were included in this review. Eighty percent of these trials were conducted in more than two different centres and were called multi-centre studies; five were international multi-centre studies conducted in high-income and low-income countries across Africa, Asia-Pacific, Europe and the Americas. Sixty-eight percent were financially supported by pharmaceutical companies.

Meta-analysis (a statistical technique that combines the results of several studies and provides a high level of evidence) suggests that children treated daily with ICS may grow approximately half a centimeter per year less than those not treated with these medications during the first year of treatment. The magnitude of ICS-related growth reduction may depend on the type of drug. Growth reduction seems to be maximal during the first year of therapy and less pronounced in subsequent years of treatment. Evidence provided by this review allows us to conclude that daily use of ICS can cause a small reduction in height in children up to 18 years of age with persistent asthma; this effect seems minor compared with the known benefit of these medications for asthma control.

Quality of evidence
Eleven of 25 trials did not report how they guaranteed that participants had an equal chance of receiving ICS or placebo or non-steroidal drugs. All but six trials did not report how researchers were kept unaware of the treatment assignment list. However, this methodological limitation may not significantly affect the quality of evidence because the results remained almost unchanged when we excluded these trials from the analysis.

Water-based exercise for adults with asthma,
Grande AJ, Silva V, Andriolo BNG, Riera R, Parra SA, Peccin MS

Asthma is a common condition in which inflammation and narrowing of the air conducting tubes may cause intermittent symptoms, possibly limiting activities of daily life. Some adults believe that exercise could trigger an asthma attack. However, research has shown the opposite—that adults who exercise may have less chance of having an asthma attack, and taking exercise in water may be more beneficial than taking exercise on land. In this review, we aimed to evaluate the effect and safety of water-based exercise for adults with asthma.

We found a total of three studies involving 136 participants with an average age between 33 and 36 years with well-controlled asthma. They underwent water-based exercise from 40 to 60 minutes three to five times a week; the programme lasted 10 to 24 weeks in two studies, and one day only in one study.

We considered data reported on quality of life, asthma general symptoms or asthma exacerbations, measure of lung function (FEV1, forced expiratory volume of the lung in the first second of air expired) and adverse events. The quality of evidence is very low because of issues with selection of participants, small number of participants, differences in exercise duration and intensity and differences in levels of asthma.
Often surrogate endpoints were measured instead of patient-important outcomes.

To sum up, more studies are needed to find out the effect and safety of water-based exercise for adults with asthma. The quality of evidence is very low because of issues with selection of participants, differences in exercise duration and intensity and differences in levels of asthma; surrogate endpoints were measured instead of patient-important outcomes.

This plain language summary is current as of 13 May 2014.

Updated & conclusions changed
March 2014-present


Inhaled hyperosmolar agents for bronchiectasis, Hart A, Sugumar K, Milan SJ, Fowler SJ, Crossingham I

Mucolytics for bronchiectasis, Wilkinson M, Sugumar K, Milan SJ, Hart A, Crockett A, Crossingham I

Ambulatory oxygen for people with chronic obstructive pulmonary disease who are not hypoxaemic at rest, Ameer F, Carson KV, Usmani ZA, Smith BJ

Tiotropium versus placebo for chronic obstructive pulmonary disease, Karner C, Chong J, Poole P

New protocols March 2014-present
Breathing exercises for children with asthma, Macêdo TMF, Freitas DA, Chaves GSS, Holloway EA, Mendonça KMPP

Effect of opioid, hypnotic and sedating medications on sleep-disordered breathing in adults with obstructive sleep apnoea, Mason M, Chong K, Smith I

Intermittent inhaled corticosteroid therapy versus placebo for persistent asthma in children and adults, Chong J, Haran C, Asher I

Intravenous magnesium sulfate for treating children with acute asthma in the emergency department, Griffiths B, Kew KM, Michell CI, Kirtchuk L

Guanylate cyclase stimulators for pulmonary hypertension, Wardle AJ, Tulloh RMR

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