Clinical review

Extracts from "Clinical Evidence"

Chronic asthma

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Interventions

Beneficial:

Inhaled short acting β_2 agonists as needed for symptom relief

Low dose, inhaled corticosteroids in mild persistent asthma

Adding inhaled long acting β_2 agonists to inhaled corticosteroids in poorly controlled asthma (for symptom control)

Likely to be beneficial:

Leukotriene antagonists for people with mild to moderate persistent asthma

Ineffective or harmful:

Regular use of β_2 agonists in mild intermittent asthma

Background

Definition Asthma is characterised by dyspnoea, cough, chest tightness, wheezing, variable airflow obstruction, and airway hyper-responsiveness. The diurnal variation of peak expiratory flow rate is increased in people with asthma. Chronic asthma is defined here as asthma requiring maintenance treatment. Asthma is classified differently in the United States and United Kingdom (box): where necessary, the text specifies the system of classification used.[1 2] Acute asthma is defined here as an exacerbation of underlying asthma requiring urgent or emergency treatment, and will be dealt with in a separate "Extract from *Clinical Evidence*."[3]

Incidence/prevalence Reported prevalence of asthma is increasing worldwide. About 10% of people have had an attack of asthma.[4 5]

Aetiology/risk factors Most people with asthma are atopic; exposure to certain stimuli initiates inflammation and structural changes in airways, causing airway hyper-responsiveness and variable airflow obstruction, which in turn cause most asthma symptoms. Stimuli include environmental allergens, occupational sensitising agents, and respiratory viral infections.[6 7]

Prognosis In people with mild asthma, prognosis is good and progression to severe disease is rare. However, as a group, people with asthma lose lung function faster than those without asthma, although less quickly than people without asthma who smoke.[8] Persistent asthma can improve with treatment. However, for reasons not clearly understood, some people (possibly up to 5%) have severe disease that responds poorly to treatment. These people are most at risk of morbidity and death from asthma.

Aims To minimise or eliminate symptoms; to maximise lung function; to prevent exacerbations; to minimise the need for medication; to minimise adverse effects of treatment; and to provide enough information and support to facilitate self management of asthma.

Outcomes Symptoms (daytime and nocturnal); lung function (peak expiratory flow rate (PEFR) and forced

Classification of severity for chronic asthma

United States

Asthma is classified by symptoms of severity. Even people with mild intermittent asthma can develop severe exacerbations if exposed to appropriate stimuli.

Mild intermittent asthma—symptoms less than weekly with normal or near normal lung function

Mild persistent asthma—symptoms more than weekly but less than daily with normal or near normal lung function

Moderate persistent asthma—daily symptoms with mild to moderate variable airflow obstruction

Severe asthma—daily symptoms and frequent night symptoms, and moderate to severe variable airflow obstruction

United Kingdom

Chronic asthma in ambulatory settings is graded according to the amount of medication required to keep symptoms controlled. People are classified stepwise according to the drugs they need for symptom control.

Step 1—occasional β agonists for relief of symptoms

Step 2—in addition, regular, inhaled anti-inflammatory agents (such as inhaled corticosteroids, cromoglycate, or nedocromil)

Step 3—in addition, high dose inhaled corticosteroids or low dose inhaled steroids plus long acting inhaled β_2 bronchodilator

Step 4—in addition, high dose inhaled corticosteroids plus regular bronchodilators

Step 5—in addition, regular oral corticosteroids

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expiratory volume in one second (FEV_1)); need for rescue medication such as inhaled β_2 agonists; variability of flow rates; activities of daily living; adverse effects of treatment.

Methods

Clinical Evidence update search and appraisal September 2000. Additional sources identified by experts.

Question What are effects of treatments for chronic asthma?

Option Regular versus as needed use of short acting inhaled β_2 agonists in adults with mild intermittent asthma

Summary Randomised controlled trials (RCTs) have found that regular use of short acting inhaled β_2 agonists in people with mild intermittent asthma provides no additional clinical benefits, compared with use as needed, and may worsen asthma control.

Benefits

We found no systematic review. We found several RCTs comparing regular against as needed inhaled salbutamol. The most recent RCT (983 people with asthma in a general practice setting, 90% using regular inhaled corticosteroids) compared as needed versus regular salbutamol (400 µg four times daily).[9] At one year, it found no significant difference between regular and as needed salbutamol in the rate of exacerbations (relative risk (RR) 0.96, 95% confidence interval 0.8 to 1.15) or in morning PEFR. Evening PEFR was significantly higher with regular salbutamol (difference 10.3 l/minute, 6.7 to 14.0), and as a consequence diurnal variation was also higher (difference 3.3%, 2.5% to 4.1%).[9] Another RCT (255 people with mild intermittent asthma taking inhaled β agonists only) compared regular and as needed salbutamol.[10] At 16 weeks, the groups did not differ significantly in symptoms, quality of life, airflow obstruction, or frequency of exacerbations. People taking regular salbutamol used more medication than those taking it as needed (total salbutamol 9.3 *v* 1.6 puffs/day) and experienced significantly greater variability in PEFR and responsiveness to methacholine. An earlier placebo controlled, double blind crossover trial (64 people taking inhaled or oral corticosteroids or inhaled cromoglycate if usually required, or both) found that most of the 57 people who had better control during active treatment periods did better with as needed than regular treatment (40 *v* 17). In addition, five of the six severe exacerbations occurred in people taking regular rather than as needed fenoterol.[11] Exacerbations were not prevented by inhaled corticosteroids.

CORDELIA MOLLOY/SPL

Harms

Two case-control studies found an association between increased asthma mortality and overuse of inhaled short acting β_2 agonists.[12,13] The evidence does not establish causality, as overusing β_2 agonists to treat frequent symptoms may simply indicate severe uncontrolled asthma in high risk individuals. Other RCTs found that regular use of inhaled β_2 agonists was associated with transient rebound deterioration in airway hyper-responsiveness after the drug was stopped[14] and increased allergen induced bronchoconstriction.[15] Tremor was commonly reported, but tolerance developed with more frequent use.[16]

Comment

In the most recent RCT, 33% of people randomised did not complete the trial, reducing the power of the RCT to detect a significant difference between regular and as needed salbutamol.[9]

Option Low doses of inhaled corticosteroids in people with mild persistent asthma

Summary RCTs have found that, in people with mild persistent asthma, low doses of inhaled corticosteroids (250-500 µg of beclomethasone dipropionate or equivalent) improve symptoms and lung function significantly more than placebo or regular β_2 agonists. We found no evidence of clinically important adverse effects in adults.

Benefits

Versus placebo: We found no systematic review. We found seven placebo controlled RCTs (1000 adults and adolescents with mild persistent asthma, using US classification; see box) evaluating low doses of inhaled budesonide,[17–20] beclomethasone,[21,22] and triamcinolone.[22–24] They all found significant improvement in lung function, symptoms, and short acting bronchodilator use compared with placebo.
Versus β_2 agonists: We found one systematic review (search date not stated, 5 small RCTs, 141 adults with mild persistent asthma using regular inhaled corticosteroids, ≤2 drugs to control asthma).[25] It found that inhaled corticosteroids significantly improved lung function (overall weighted effect size for PEFR 0.59, 0.32 to 0.84). One RCT not included in the review (103 adults with mild asthma, diagnosed within 12 months, not using oral corticosteroids) found that inhaled budesonide 1200 µg/day compared with inhaled β_2 agonists persistently and significantly improved all outcomes over two years (no confidence intervals available).[26]

Harms

We found no published evidence that low doses of inhaled corticosteroids (< 1000 µg/day of beclomethasone dipropionate or equivalent) cause important systemic effects in adults.[27] Although posterior subcapsular cataracts are more common in people taking oral corticosteroids,[28] most studies in adults provide no evidence that inhaled

corticosteroids increase the risk once the confounding effect of oral corticosteroids is removed.[29] However, one recent population based case-control study found that, in older people, inhaled high dose beclomethasone dipropionate was associated with a slightly greater risk of nuclear cataracts (RR 1.5, 1.2 to 1.9) and posterior subcapsular cataracts (RR 1.9, 1.3 to 2.8).[30] We found no published reports of an increased risk of osteoporosis or fractures. Inhaled corticosteroids can cause oral candidiasis, dysphonia, and bruising, but these are troublesome in fewer than 5% of people.[31 32]

Comment

The results of the systematic review should be interpreted with caution as the few small RCTs included neither consistently measured PEFR at the same time of the day nor reported morning and evening PEFRs.[25] The case-control study on cataract formation did not allow for the confounding effect of allergy,[30] which is also a risk factor for cataract development.[33]

Option Addition of long acting inhaled β_2 agonists in people whose asthma is poorly controlled by inhaled corticosteroids

Summary One systematic review and one additional RCT have found that, in people with poorly controlled asthma, adding regular doses of long acting, inhaled β_2 agonists to inhaled corticosteroids improves symptoms and lung function. Unlike regular use of short acting β_2 agonists, regular use of long acting β_2 agonists has not been linked to deterioration in asthma control. We found no good evidence relating to their effect on mortality.

Benefits

Versus placebo: We found no systematic review. We found two RCTs (506 and 217 people with moderate, persistent asthma, which was not controlled with inhaled corticosteroids 250-2000 µg/day beclomethasone or equivalent)[34 35] comparing regular, long acting inhaled β_2 agonists and placebo. These trials found that twice daily salmeterol or formoterol improved quality of life scores, PEFR, and FEV_1 more than placebo. Exacerbation rates were not significantly different between the two groups in either trial.
Versus increased use of inhaled corticosteroids: We found one systematic review[36] and one additional RCT.[37] The review (search date 1999, 9 double blind RCTs, 3685 people with symptomatic asthma on their current dose of inhaled steroids, duration 3-6 months) compared adding salmeterol against increased use of inhaled corticosteroids (at least double the usual dose). It found that morning PEFR was significantly higher with salmeterol (3 months: weighted mean difference (WMD) in PEFR 22 l/minute, 15 to 30, $P < 0.001$; 6 months: WMD 28 l/minute, 19 to 36). Salmeterol compared with higher dose corticosteroids significantly increased days without symptoms (WMD at 6 months: 15, 12 to 18) and nights without symptoms (WMD at 6 months: 5, 3 to 7). Salmeterol compared with higher dose corticosteroids also significantly reduced the need for rescue medication. No increase in asthma exacerbations of any severity was found in the salmeterol group.[36] The additional RCT (852 people taking low to moderate dose inhaled corticosteroids) found that additional twice daily formoterol plus as needed terbutaline compared with no additional treatment significantly improved symptoms and lung function and reduced exacerbations.[37] Exacerbations were reduced further by a fourfold increase in daily dosage of inhaled corticosteroid, and further still by combined, higher dose of budesonide plus formoterol.

DAMIEN LOVEGROVE/SPL

Harms

Several studies have found that people taking regular doses of long acting inhaled β_2 agonists develop tolerance to protection against bronchoconstriction[38–40] and may develop a tremor. Short acting inhaled β_2 agonists are associated with deterioration in asthma control and increased risk of death.[11–13] Regular use of long acting inhaled β_2 agonists has not been linked to deterioration in asthma control.

Comment

We found no RCTs or other studies with sufficient power to assess the effect of regular use of long acting inhaled β_2 agonists on death rates.[41]

Option Leukotriene antagonists in adults with mild to moderate persistent asthma

Summary RCTs have found that leukotriene antagonists compared with placebo added to β_2 agonists significantly reduced asthma symptoms and use of β_2 agonists. One systematic review found no significant difference in the rate of exacerbations between leukotriene antagonists compared with inhaled corticosteroids, but inhaled corticosteroids significantly increased quality of life, lung function, and symptom control.

Benefits

Versus placebo: We found no systematic review. We found three RCTs (1300 adults with asthma taking β_2 agonists alone) which compared the addition of leukotriene antagonists or placebo for 13 weeks.[42–44] The RCTs found consistently that zafirlukast (20 mg twice daily) compared with placebo significantly reduced daytime and night time asthma symptoms and use of β_2 agonists. The largest RCT (762 people) found that zafirlukast compared with placebo significantly reduced daytime symptoms, night time awakenings, and use of β_2 agonists (3.9 *v* 3.1 puffs per day; $P < 0.01$).[42] Morning FEV_1 was significantly increased in people taking zafirlukast (morning FEV_1 improved by 7% *v* 3%, $P < 0.01$).[42]
Versus inhaled corticosteroids: We found one systematic review (search date 1999, 8 RCTs, >2000 adults with asthma),[45] and one subsequent RCT.[45] The review compared various leukotriene antagonists with inhaled corticosteroids for 6-12 weeks. Doses of corticosteroids were equivalent to beclomethasone 250 µg to 400 µg daily. The review found no significant difference between leukotriene antagonists and corticosteroids in the number of people with exacerbations who required systemic steroids (4 RCTs, RR 1.3, 0.9 to 1.9). However, corticosteroids compared with leukotriene antagonists significantly improved lung function (FEV_1: 3 RCTs, standardised mean difference (SMD) 0.3, 0.2 to 0.4), morning PEFR (3 RCTs, SMD 0.4, 0.2 to 0.5), quality of life (3 RCTs,

WMD 0.3, 0.1 to 0.4), symptoms (3 RCTs, SMD 0.3, 0.2 to 0.4), and night awakenings (2 RCTs, WMD 0.6, 0.3 to 0.9) and reduced the need for rescue β_2 agonists (3 RCTs, SMD 0.3, 0.2 to 0.4).[45] The subsequent RCT (451 adults with asthma, previously treated with β_2 agonists alone) compared fluticasone 88 mg with zafirlukast 20 mg, both twice daily for 12 weeks.[46] The RCT found results consistent with the systematic review for exacerbations, lung function, day and night symptoms, and use of rescue β_2 agonists.

Harms

In the RCT comparing zafirlukast and placebo, the incidence of adverse effects (predominantly pharyngitis and headache) was similar in both groups (350/514 (68%) *v* 160/248 (65%)).[42] The systematic review found that adverse effects were not significantly different with leukotriene antagonist compared with corticosteroids, but leukotriene antagonists significantly increased the risk of "withdrawals for any cause" (RR 1.4, 1.1 to 1.9), and "withdrawals due to adverse effects" (RR 1.9, 1.1 to 3.3).[45]

Comment

The systematic review found that few RCTs providing results about specific outcomes and included few unpublished trials. The results should therefore be interpreted cautiously.

Competing interests: None declared.

Glossary

Diurnal variation A characteristic of people with asthma is increased variation in peak flow rates and FEV_1 during the day. The diurnal variation is sometimes expressed as the difference between maximum and minimum values expressed as a fraction of the maximum value.
Forced expiratory volume in one second (FEV_1) The volume breathed out in the first second of forceful blowing into a spirometer, measured in litres.
Peak expiratory flow rate (PEFR) The maximum rate that gas is expired from the lungs when blowing into a peak flow meter or a spirometer. It is measured at an instant, but the units are expressed as litres per minute.
Salbutamol A short acting β_2 agonist known as albuterol in the United States.

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