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Evidence Report/Technology Assessment

Number 44

Management of Chronic Asthma

Summary

Overview

Asthma is a heterogeneous clinical disorder characterized by episodic wheezing, chronicity, hyperresponsiveness of airways to a variety of stimuli, and largely reversible obstruction of airways. Inflammation is present in the airways and, over time, airway remodeling may occur, which may, in turn, cause permanent structural changes and decline in lung function. Asthma is classified by four levels of severity: mild intermittent, mild persistent, moderate persistent, and severe persistent.

Asthma is estimated to affect 14 to 15 million persons in the United States. It is the most common chronic disease of childhood, affecting approximately 4.8 million children. There are 70,000 asthma-related hospitalizations each year, and more than 5,000 people die of asthma annually. Hospitalization rates have been highest among blacks and children, and death rates have been consistently highest among blacks 15 to 24 years of age.

This report is the product of a systematic literature review of the evidence on five key questions related to the management of chronic asthma. These key questions were selected as high priority issues by the three partner organizations that nominated this topic to the Agency for Healthcare Research and Quality (AHRQ) for development of an evidence report. The nominating organizations were the National Heart, Lung, and Blood Institute (NHLBI), the American Academy of Pediatrics (AAP), and the American Academy of Family Physicians (AAFP).

The five key questions addressed in this systematic review of evidence are:

1. Whether chronic use of inhaled corticosteroids (ICS) improves long-term outcomes for children with mild-to-moderate asthma, and whether chronic use of ICS results in long-term adverse effects in children.
2. Whether, for patients with mild-moderate asthma, early initiation of long-term control medication (i.e., ICS) prevents asthma progression.
3. Whether, for patients with moderate asthma, adding other long-term controller medications (i.e., leukotriene modifiers, long-acting beta-2 agonists, or theophylline) to low-moderate dosages of ICS improves control or lowers ICS dosage.
4. Whether adding antibiotics to standard care improves the outcomes of treatment for acute exacerbation of asthma.
5. Whether addition of a written asthma action plan to medical management alone improves outcomes, and whether a peak flow monitor-based plan is superior to a symptom-based plan.

Reporting the Evidence

As outlined, the results of this systematic review are reported in five parts that reflect the five key questions. Each key question states the patient populations and interventions of interest.

A description of the outcomes of interest follows the outline of key questions.

Part 1. Long-Term Management of Asthma in Children

Key Question 1a. Does chronic use of ICS improve long-term outcomes for children with mild-to-moderate asthma, compared to:

- "As needed" beta-2 agonists.
- Long-acting beta-2 agonists.
- Theophylline.
- Cromolyn/nedocromil.
- Combinations of the above drugs.

Key Question 1b. What are the long-term adverse effects of chronic ICS use in children on the following outcomes:

- Vertical growth.
- Bone mineral density (BMD).
- Ocular toxicity.
- Suppression of adrenal/pituitary axis.

Part 2. Effects of Delayed ICS Use on Progression and Reversibility

Key Question 2. For patients with mild-to-moderate asthma, does early initiation of long-term controller therapy (i.e., ICS) prevent progression of asthma, as indicated by changes in lung function or severity of symptoms?

Part 3. Addition of Other Long-Term Controller Medications to ICS

Key Question 3. For patients with moderate asthma who are receiving ICS, does adding another long-term control agent improve outcomes? Three questions are of interest:

a. Does addition of a long-term controller improve asthma control attained with a fixed dose of ICS?

b. Does addition of a long-term controller maintain or improve asthma control while titrating ICS to the lowest effective dose?

c. Does addition of a long-term controller maintain or improve asthma control as compared with increasing the ICS dose?

Long-term control agents of interest are:

- Long-acting beta-2 agonists.
- Theophylline.
- Leukotriene antagonists.
- Cromolyn/nedocromil.

However, there were no studies of cromolyn/nedocromil added to ICS that met study selection criteria for this review.

Part 4. Effect of Antibiotics on Acute Asthma Exacerbations

Key Question 4a. Does routinely adding antibiotics to standard care improve the outcomes of treatment for acute exacerbation of asthma?

Key Question 4b. Does the addition of antibiotics to standard care improve the outcomes of treatment for an acute exacerbation of asthma in the following populations:

- Patients without signs and symptoms of a bacterial infection.
- Patients with signs and symptoms of a bacterial infection.
- Patients with signs/symptoms of sinusitis?

Part 5. Asthma Management Plans

Key Question 5a. Compared to medical management alone, does the use of a written asthma action plan improve outcomes?

Key Question 5b. Compared to a written action plan based on symptoms, does use of a written action plan based on peak flow monitoring improve outcomes?

Evidence also was sought to address the following additional questions, but no studies that met the study selection criteria were found.

- What are the outcomes of a written action plan for daily use compared to a written action plan for exacerbation use only?
- What are the outcomes of peak flow monitoring without an action plan compared to medical management alone?
- What are the outcomes of chronic peak flow monitoring compared to exacerbation-only peak flow monitoring?
- What are the relative outcomes of alternative schedules of peak flow monitoring?

Outcomes Reported

For each of the five key questions, data was sought on lung function outcomes, symptom outcomes, and utilization outcomes. Lung function measures included spirometric measures (pre- or post-bronchodilator forced expiratory volume in 1 second [FEV1]); peak flow meter (PFM) measurement of peak expiratory flow (PEF); and measures of bronchial hyperresponsiveness. Post-bronchodilator FEV1 was judged to be the best measurement of long-term changes in lung function and, therefore, the best indicator of disease progression in asthma. Symptom outcomes included symptom scores, symptom frequency, use of acute bronchodilator medication, exacerbations, and use of oral corticosteroids. Quality-of-life data, although reported infrequently, were also collected in this systematic review. Utilization outcomes included hospitalizations, emergency room visits, unscheduled visits, and measures of days lost from school or work.

Review of treatment-related adverse effects was limited to Key Questions 1 and 3. Key Question 1 reports only on children and is limited to long-term adverse effects related to vertical growth, BMD, ocular toxicity, or suppression of adrenal/pituitary axis. Key Question 3 summarizes only the short-term adverse events that were reported in the reviewed studies of addition of long-acting beta-2 agonists, theophylline, or leukotriene antagonists to ICS. Adverse events of interest were: headache; central nervous system (CNS) morbidity (e.g., seizures) and tremors; cardiac dysfunction; gastrointestinal (GI) dysfunction (i.e., dyspepsia, nausea, vomiting, diarrhea); upper respiratory infections or sinusitis; throat irritation, hoarseness, or unpleasant taste; sleep disorders; and hepatic toxicity.

Methodology

The protocol for this review was prospectively designed to define: study objectives, search strategy, patient populations of interest, study selection criteria and methods for determining study eligibility, outcomes of interest, data elements to be abstracted and methods for abstraction, and methods for assessment of study quality. Two independent reviewers reviewed studies for inclusion and abstracted data from included studies. Detailed printed directions for consistent data abstraction were provided to all reviewers. Substantive disagreements were few, and they were resolved by consensus.

The development of the evidence report was subject to extensive expert review. A technical advisory group (TAG) of eight nationally recognized experts provided ongoing guidance on all phases of this project. The partner organizations (i.e., the NHLBI, the AAFP, and the AAP) each designated TAG members.

The draft report was also reviewed by a panel of 15 external reviewers (experts and stake-holders were included). Four reviewers were invited to the panel by the Technology Evaluation Center (TEC) under the auspices of this task order for their expertise in pediatrics, asthma, and systematic review methodology. Eight of the external reviewers were appointed by professional organizations: the American Medical Association; American Lung Association; American College of Chest Physicians; American College of Emergency Physicians; American Society of Health-System Pharmacists; National Medical Association; American College of Asthma, Allergy, and Immunology; and the American Academy of Pediatrics. One external reviewer represented the National Institute of Allergy and Infectious Diseases of the National Institutes of Health, and two external reviewers represented the pharmaceutical industry.

Both MEDLINE® and EMBASE databases were searched using PubMed® (National Library of Medicine). The search included all articles published from January 1980 to August 2000 that included at least one of the following textwords (tw) or Medical Subject Headings (MeSH®) terms in their titles, their abstracts, or their keyword lists:

- Leukotriene antagonists (including all MeSH® terms under this heading) OR zileuton (tw) OR montelukast (tw) OR zafirlukast (tw) OR cromolyn (tw) OR nedocromil (tw) OR theophylline (including all MeSH® terms under this heading) OR albuterol (MeSH®) OR albuterol (tw) OR salmeterol (tw) OR flunisolide (tw) OR fluticasone (tw) OR beclomethasone (tw) OR budesonide (tw) OR dexamethasone (tw) OR triamcinolone (tw) OR steroids (including all MeSH® terms under this heading).
- Adrenergic beta-agonists (including all MeSH® terms under this heading) OR albuterol (tw) OR bitolterol (tw) OR isoetharine (tw) OR isoproterenol (tw) OR metaproterenol (tw) OR orciprenaline (MeSH®) OR pirbuterol (tw) OR terbutaline (tw) OR ipratropium (tw) OR adrenal cortex hormones (including all MeSH® terms under this heading).
- (Peak expiratory flow rate (MeSH®) OR (peak (tw) AND flow (tw))).

- (Meter (tw) OR meters (tw) OR monitor (tw) OR monitors (tw) OR monitoring (tw).
- (Action (tw) AND (plan (tw) OR plans (tw))) OR self care (MeSH®) OR patient care planning (MeSH®) OR patient participation (MeSH®).
- Beclomethasone (tw) OR budesonide (tw) OR dexamethasone (tw) OR flunisolide (tw) OR fluticasone (tw) OR triamcinolone (tw).
- Leukotriene antagonists (including all MeSH® terms under this heading) OR zileuton (tw) OR montelukast (tw) OR zafirlukast (tw).
- Cromolyn (tw) OR nedocromil (tw).
- Theophylline (including all MeSH® terms under this heading).
- Adrenergic beta-agonists (including all MeSH® terms under this heading) OR orciprenaline (MeSH®) OR albuterol (tw) OR bitolterol (tw) OR isoetharine (tw) OR isoproterenol (tw) OR metaproterenol (tw) OR pirbuterol (tw) OR terbutaline (tw) OR salmeterol (tw).
- Antibiotics (including all MeSH® terms under this heading).
- The search results were then limited to include only those articles that were indexed under the MeSH® term asthma (including all MeSH® terms under this heading) OR asthma (tw), that addressed studies on human subjects, and that were indexed under any of the following study design terms:
  - Clinical trials (including all MeSH® terms under this heading) OR intervention studies (MeSH®) OR double-blind method (MeSH®) OR single-blind method (MeSH®) OR placebos (MeSH®) OR random allocation (MeSH®).
  - Controlled clinical trial OR document type=randomized controlled trial.
  - Control? (truncated tw) OR placebo? (truncated tw) OR random? (truncated tw) OR blind? (truncated tw).
  - Cohort studies (MeSH®).

To supplement the strategy, the abstracts presented at the year 2000 meeting of the American Thoracic Society also were searched. Additional articles were also identified by TEC staff or by TAG members.

Total retrieval was 4,235 English and 343 non-English references. A total of 647 full-length journal articles in English were retrieved after the abstract review. Each study was initially assessed for potential to address any of the topics of interest, and reviewed against all potentially relevant study selection criteria. A further 21 articles in languages other than English but with an English-language abstract were also reviewed, and two were selected for inclusion. A total of 87 articles met the study selection criteria for inclusion in this systematic review.

This is a systematic review of published evidence. Criteria that were specific to each key question were developed for selecting studies for inclusion in this review. For assessment of efficacy outcomes, inclusion was limited to controlled trials, as many characteristics of asthma patients (e.g., disease severity, treatment compliance, concurrent treatments) are likely to affect the outcomes of interest. Most of the included trials were randomized, but nonrandomized controlled trials were also included. Uncontrolled studies were excluded, except for the review of long-term adverse effects of ICS in children.

A supplementary meta-analysis accompanies this full systematic review. Meta-analyses of the addition of long-acting beta-2 agonists to either a fixed ICS dose or to a lower ICS dose (in comparison with an increased ICS dose alone) were conducted for the following outcomes: FEV1 and PEF lung function outcomes, and puffs per day of short-acting beta-2 agonist usage. Meta-analyses of other outcomes of interest were considered, but were not possible due to variability in reporting or lack of sufficient data. There were insufficient data to perform meta-analysis for studies of the addition of theophylline or leukotriene antagonists to ICS. There were also insufficient data to perform meta-analysis for any other key questions in this systematic review.

Combined analyses were performed using the random effects, empirical Bayes model. Studies of FEV1 outcomes and PEF outcomes were combined on the basis of calculated effect size so that studies reporting in either liters or percent predicted (for FEV1) and L/min or percent predicted (for PEF) could be pooled. Nonrandomized studies, studies of

children, and studies where effect size could not be calculated for FEV1 or PEF outcomes were excluded from combined analysis. A sensitivity analysis was performed for higher-quality studies. Trials that were double-blinded, met defined thresholds for minimizing exclusions from analysis, and met at least four of six asthma-specific quality indicators were defined as higher quality for purposes of sensitivity analysis. Studies were also stratified into two levels for each of four potentially confounding variables: baseline ICS dose, treatment duration, mean patient age, and mean baseline FEV1 as a surrogate for baseline disease severity.

Findings

Part 1. Long-Term Management of Asthma in Children

Key Question 1a. Does chronic use of ICS improve long-term outcomes for children with mild-to-moderate asthma?

- Compared to as-needed beta-2 agonists without long-term controller medication, use of ICS improves control in children with mild-to-moderate asthma.

The evidence on the efficacy of ICS in children older than 5 years is from six trials, five of which were placebo controlled and randomized. These six trials enrolled a total of 790 patients treated with ICS and 652 controls. The most robust evidence came from the recent Childhood Asthma Management Program Research Group (CAMP) trial, which contributed 40 percent of ICS patients (n=311) and 64 percent of controls (n=418) to this review. It had the longest duration of treatment (4 years), the most complete outcome measures, and the most detailed reporting of study design and statistical analysis.

ICS-treated patients demonstrated improvement in prebronchodilator FEV1, reduced airway hyperresponsiveness, improvement in symptom scores and symptom frequency, less supplemental albuterol use, fewer courses of oral corticosteroids, and lower utilization (e.g., hospitalization).

Two small trials (n=69) compared ICS treatment to placebo in children under 5 years of age. The available evidence is scant, but the reported results appear to be consistent with those reported for children over 5 years of age.

- The evidence does not suggest that ICS use improves long-term postbronchodilator FEV1.

The CAMP trial reported no difference in the change in postbronchodilator FEV1, which is a measure of disease progression, after 4 years of treatment.

- No alternative long-term controller medication appears to be superior to ICS.

The CAMP trial found no difference between nedocromil and placebo in lung function or symptom outcomes, although courses of oral steroids and urgent care visits were reduced. Therefore, it can be concluded that ICS are more effective than nedocromil in reducing the frequency and severity of symptoms, supplemental beta-2 agonist use, and the frequency of hospitalizations due to asthma.

The available evidence is not adequate to determine the relative effectiveness of ICS and salmeterol. Two randomized and double-blinded trials enrolled 116 (99 evaluable) patients treated with ICS, 112 (83 evaluable) patients treated with salmeterol, and 80 (55 evaluable) patients treated with placebo. Although the evidence is insufficient to permit conclusions, of the statistically significant results reported, all favored ICS over salmeterol.

One trial (n=195) compared ICS use to theophylline. Because of the lack of additional trials and large numbers of withdrawals, the data are not sufficient to compare the relative effectiveness of ICS and theophylline.

Key Question 1b. What are the long-term adverse effects of chronic ICS use in children on vertical growth, BMD, ocular toxicity, and suppression of adrenal/pituitary axis?

- The available evidence suggests that the use of ICS at recommended doses does not have frequent, clinically significant, or irreversible effects on any of the outcomes reviewed, at least over the short term. It is possible that chronic use of ICS initiated in childhood might have cumulative effects that increase the relative risk of certain events (such as osteoporosis or glaucoma in later life). However, none of the available studies have sufficient followup duration or patient numbers to assess this possibility.
- Evidence on growth velocity over 1 year consistently shows a difference of average height of 1 cm/year between children treated with ICS and controls. However, the cumulative difference in growth appears to

be much less than would be expected if the growth velocity difference had been maintained over several years. In the only randomized controlled trial with 4- to 6-year followup, the difference in cumulative growth was still approximately 1 cm at the end of the study.

Evidence on three measures of vertical growth in children was found: short-term growth velocity measured over a period of 1 year or less; growth velocity and change in height measured over longer duration (4-6 years); and final attained adult height. The evidence on short-term growth velocity is from a published meta-analysis which pooled data from five randomized controlled trials, representing 855 subjects, with a mean age of 9.5 years. Evidence on growth velocity and height over longer duration is from the CAMP trial comparing ICS, nedocromil, and placebo in 1,041 children with mild-to-moderate asthma (followed for 4 to 6 years). For final attained adult height, evidence is from three retrospective cohort studies that adjusted for the potential confounding factor of parental height. Together, these three studies included a total of 243 asthmatics treated with ICS, 154 asthmatics who had not been treated with ICS, and 204 nonasthmatic controls.

Evidence on growth velocity over 1 year is consistent in showing a difference of average height of 1 cm/year between children treated with ICS and controls. In the only trial extending beyond 1 year, a difference consistent with this magnitude also occurred in the first year of the study. However, in subsequent long-term followup, the difference in growth velocity was not maintained. At the end of the 4- to 6-year observation period, there was still an approximately 1 cm difference in cumulative growth between the study groups.

The evidence on final adult height appears to be fairly consistent, as well. However, this evidence is based on retrospective cohort studies, which are subject to selection bias and the confounding effects of severity of asthma cannot be adjusted for. Some comparisons in these studies were also limited by small sample size. One study showed a difference in final attained adult height between ICS users and nonusers. However, the difference is much less than would be expected if a 1 cm/year growth velocity difference was maintained over several years.

- Treatment with ICS does not affect BMD when given in usual doses over 4 to 6 years of observation.

The CAMP study followed a population of mild-to-moderate asthmatics, mean age approximately 9 years, treated for 4 years with ICS. This study, with its large numbers and randomization and assessment of longitudinal changes, provides very strong evidence that there is no effect of ICS on BMD (in the doses given and time duration provided). One retrospective study of 30 young adults found a significant correlation between BMD and ICS dosage among female patients. Such studies are subject to potential confounding because of unmeasured differences between groups that are risk factors for low BMD. In addition, the clinical significance of any observed differences in BMD is unknown. Subtle differences in BMD would not have clinical impact until added to other risk factors such as aging, and it is uncertain whether differences observed during young adulthood would persist to old age. Alternatively, it is possible that subtle changes during critical periods of bone mineral accretion (occurring in childhood) could magnify the risk of osteoporotic fracture in later life.

- The evidence shows no effects of ICS on development of posterior subcapsular cataract or glaucoma, but the population size and duration of the available studies are limited.

Studies that report the occurrence of posterior subcapsular cataracts consist mostly of small cohorts and cross-sectional studies, with the exception of the CAMP study. The expected incidence rate of subcapsular cataract in any population of normal young children and adults is zero. These studies are sufficient to rule out a large effect of ICS on the incidence of cataract, but are not capable of detecting a small increase in risk of an event which has a baseline risk of essentially zero. Also, several of the clinical trials that evaluated the development of cataracts were of relatively short duration.

Two of these studies also reported on measurements of ocular pressure. The available and very limited data show no relationship between glaucoma or raised intraocular pressure and ICS.

- The overall evidence shows only clinically insignificant effects of ICS on the HPA axis. However, there may be persons acutely susceptible to these effects.

Two types of evidence on the effects of ICS on hypothalamic-pituitary-adrenal (HPA) axis function were

found. These were case reports of iatrogenic Cushing's syndrome related to ICS and six studies (n=413 treated with ICS) regarding HPA axis function. Each study evaluated from one to three different measures of HPA function, with followup for at least 1 year after initiation of treatment.

The case reports show that systemic effects can occur in clinically detectable ways in patients, with a strong case for causality in these individual patients by the accompanying laboratory tests and response when ICS were withdrawn. In the controlled clinical studies that used more sensitive tests of cortisol such as 24-hour urinary cortisol, two out of three studies of HPA axis function showed a statistically significant effect of ICS. It should be noted that these statistically significant results occur as comparisons of mean values between groups. Few or no patients in most studies have laboratory values out of the "normal" range. However, the clinical significance of these more sensitive indicators of adrenal function is unknown.

The case reports appear to be reasonably causally attributable to ICS based on clinical presentation, consistency with laboratory findings, and clinical response to reduction or withdrawal of treatment. Although the studies show that, on average, patients may have only clinically insignificant effects of ICS on the HPA axis, there may be other patients acutely susceptible to their effects.

Part 2. Effects of Delayed ICS on Progression and Reversibility in Patients With Mild-to-Moderate Asthma

- The evidence is insufficient to permit conclusions on whether early intervention with long-term controller medications is superior to delayed introduction. The best available evidence does not support the assumption that mild-to-moderate asthmatics have a progressive decline in lung function that can be prevented by early initiation of ICS.

The CAMP trial is the most robust evidence to date on long-term lung function outcomes in a group of patients treated with ICS compared with a placebo-control group. Although immediate initiation and delayed initiation of ICS were not directly compared, CAMP provides the strongest prospective evidence available on the natural history of mild-to-moderate asthma managed without ICS or other long-term controller medication. The CAMP trial did not find progressive decline in lung function over a 4-year period in a population of children with mild-to-moderate asthma managed without ICS; nor was there a significant difference or change between treated and control groups in postbronchodilator FEV1.

It is possible that the findings of the CAMP study are not generalizable to patients with less intensive overall care. Also, the findings may not be generalizable over longer periods of followup, to populations newly diagnosed with asthma, to groups of patients with more severe asthma, or to a subset of patients with a more variable disease course. But, for the general group of children with mild-to-moderate asthma, there is no convincing evidence that a progressive and clinically measurable decline in lung function can be altered by early initiation of ICS.

The available evidence on immediate vs. delayed initiation of ICS is from four studies. These studies have notable limitations with respect to relevance of the population, time frames for study entry and followup, clarity of reporting, and the use of appropriate control groups. None of these studies was prospectively designed to address the key question in the specific population of interest and thus, did not provide rigorous data relevant to this particular key question. Two studies (n=52; n=102, respectively) were open-label extensions of randomized controlled trials on the efficacy of ICS, in which the patients initially assigned to the control group were subsequently treated with ICS. There were also two single-arm studies, one of adults (n=105) and one of children (n=216), in which patients were stratified by duration of asthma prior to initiating ICS treatment (with outcomes being compared across the strata).

Due to high withdrawal rates, the most relevant of the extension phase randomized trials reported only on 16 patients who received immediate corticosteroid treatment; and no data were provided to test the statistical significance of results at the final 3-year time point. The larger of the extension phase randomized trials did not report on the patient population and outcomes most relevant to the key question. Neither of the single-arm studies clearly demonstrated a relationship between asthma duration and outcomes that was consistent among all strata analyzed.

Part 3. Addition of Other Long-Term Controller Medications to ICS in Patients With Moderate Asthma

- There is a large body of evidence on the addition of long-acting beta-2 agonists to ICS, consisting of 28 studies that enrolled over 7,000 patients, with 1-year followup in the longest trials. The evidence consistently shows improvement in lung function outcomes,

symptom outcomes, and supplemental beta-2 agonist use. Limited evidence shows that ICS dosage may be reduced without diminishing asthma control. However, there are only two pediatric studies that together report on 383 children, only 167 of whom were treated with the addition of long-acting beta-2 agonists.

Sixteen randomized, double-blinded trials that enrolled a total of 3,163 patients compared the addition of long-acting beta-2 agonists to a fixed dose of ICS. This evidence consistently showed improvement in lung function outcomes, symptom outcomes, and supplemental beta-2 agonist use. The combined estimate of treatment effect for FEV1 is 0.17 L (95 percent CI, 0.12–0.22) or 3.71 percent predicted (95 percent CI, 2.67–4.75), based on 14 studies with 2,781 evaluable patients. For morning, patient-measured PEF, the combined estimate of treatment effect is 24.7 L/min (95 percent CI, 17.7–31.7) or 7.3 percent predicted (95 percent CI, 5.3–9.3), based on nine studies with 1,678 evaluable patients. For supplemental beta-2 agonist use, the combined estimate of treatment effect was 1.18 fewer puffs/day (95 percent CI, 1.56–0.84), based on six studies with 1,142 evaluable patients.

Three crossover trials that enrolled a total of 151 patients evaluated reducing the dose of ICS after the addition of long-acting beta-2 agonists compared to placebo. The largest of these trials, which was randomized and double-blinded, reported on 84 patients treated for 6 months. All three trials demonstrated statistically significant reductions in ICS dosage for the long-acting beta-2 agonist group, ranging from 13.5 percent to 23.4 percent less than placebo. The evidence suggests that the reduction in dose is achieved without diminishment of lung function or increase in symptoms; and there is limited evidence to suggest improvement in symptoms.

Twelve randomized trials that enrolled more than 4,000 patients compared the addition of a long-acting beta-2 agonist to low or moderate dose ICS with an increased dose of ICS. All trials but one were double-blinded. This evidence consistently showed improvement in lung function outcomes, symptom outcomes, and supplemental beta-2 agonist use. The combined estimate of the magnitude of treatment effect for FEV1 is 0.11 L (95 percent CI, 0.07–0.15) or 2.32 percent predicted (95 percent CI, 1.48–3.16), based on eight studies with 2,754 evaluable patients. For morning, patient-measured PEF, the combined estimate of treatment effect is 11.6 L/min (95 percent CI, 5.2–18.0) or 3.4 percent predicted (95 percent CI, 1.5–5.3), based on 10 studies with 3,042 evaluable patients. For supplemental beta-2 agonist use, the combined estimate of treatment effect was 0.19 fewer puffs/day (95 percent CI, 0.06–0.31), based on three studies with 725 evaluable patients.

Data on adverse events were abstracted from clinical trials selected for inclusion in this report. In general, the adverse event profile for the addition of long-acting beta-2 agonists was similar to that for ICS alone. This analysis is limited because it examines only short-term adverse events for patients enrolled in clinical trials.

- There is a small body of evidence on the addition of theophylline, consisting of six studies that enrolled 408 patients. The evidence suggests that the addition of theophylline to ICS produces improved lung function and symptoms. However, there are only two pediatric studies available that together reported on only 47 children treated with theophylline.

Six studies that evaluated a total of 408 patients compared the addition of theophylline to ICS, with 6 months of treatment in the longest trial. Four of these compared the addition of theophylline to a fixed ICS dose, and two compared the addition of theophylline to a higher dose of ICS. The four studies on the addition of theophylline to fixed ICS dose are generally mixed in their results, but the qualitative direction of the results suggests that the addition of theophylline to a fixed ICS dose produces improved lung function and symptoms. Based on two randomized clinical trials, theophylline plus ICS vs. a higher dose of ICS appears to produce roughly equivalent improvements in lung function and symptoms.

- The evidence on the addition of leukotriene antagonists to ICS consists of five studies that enrolled a total of 1,111 patients, with 4 months of treatment in the longest trial. The evidence shows improved lung function and symptom scores when leukotriene antagonists are added to ICS. One trial showed that ICS dosage may be reduced without diminishing asthma control. There are no pediatric studies available.

Five studies enrolling 1,111 patients compared the addition of leukotriene antagonists to ICS. These studies are mostly randomized controlled trials that report on short-term outcomes. Four studies compared the addition of a leukotriene antagonist to a fixed dose ICS, and the fifth one evaluated the ability to reduce the ICS dose after starting a leukotriene antagonist. Of the four studies using a fixed dose of ICS, all showed that lung function was better when a leukotriene antagonist was added to a fixed dose of ICS. Three of these four studies also showed that symptom scores were improved. Two of the studies showed decreased use of beta-2 agonist under the combined regimen. The fifth study showed that the addition of a leukotriene antagonist allowed a greater number of patients to reduce the dosage of ICS under protocol-guided dosing guidelines.

Part 4. Effect of Antibiotics on Acute Asthma Exacerbations

- The limited available evidence suggests that there is no benefit of using antibiotics routinely, or when suspicion of bacterial infection is low. No study addressed whether using antibiotics when suspicion of bacterial infection is moderate or high improves the outcome of treatment for acute exacerbation of asthma.

The available evidence consists of two randomized, placebo-controlled trials that enrolled a total of 121 hospital admissions for acute asthma exacerbations. Both studies were relatively old, having been published in 1974 and 1982. Furthermore, they may have been underpowered to detect treatment differences. One of the studies evaluated lung function and symptom outcomes only at 24 hours after patient admission, a length of time that may be insufficient to evaluate the benefit of antibiotics. In addition, the antibiotics used in these studies did not have activity against atypical organisms, such as mycoplasma or chlamydia. It is not known whether antibiotics in current use that have activity against atypical organisms may improve outcomes.

The available evidence suggests that there is no benefit of using antibiotics routinely or when suspicion of bacterial infection is low. Neither study found a statistically significant benefit for antibiotics on the outcomes of lung function at time of discharge, hospital length-of-stay, or symptom scores. There were no studies that addressed the question of greatest relevance to contemporary clinical practice, whether using antibiotics when suspicion of bacterial infection is moderate or high (i.e., when signs and symptoms suggest the possibility of bacterial infection, but do not clearly indicate its presence) improve the outcomes of treatment for acute exacerbation of asthma.

Part 5. Asthma Management Plans

- The available evidence is insufficient to demonstrate that, compared to medical management alone, the use of a written asthma action plan improves outcomes. The available evidence is also insufficient to demonstrate that, compared to a written action plan based on symptoms, use of a written action plan based on peak flow monitoring (PFM) improves outcomes.

A large body of literature on self-management interventions in asthma was reviewed for this report. From this literature, randomized controlled trials were selected that contained specific comparisons relevant to the key question. These trials were also largely free of contamination by interventions that were not directly relevant to the key question. Many articles were excluded due to the presence of multimodal interventions in the treatment group, particularly intensive patient education or optimization of medications, which were likely to confound results.

Nine randomized controlled trials that enrolled a total of 1,501 patients met the study selection criteria for this key question. Two of these trials included three arms: medical management alone, PFM-based written action plan, and symptom-based written action plan. This resulted in 11 comparisons among the nine studies. Seven trials (n=1,079) compared medical management with and without a written action plan (all having used a PFM-based plan). The two types of written action plans (PFM-based and symptom-based) were compared in four trials (n=393).

Of the nine trials reviewed, seven reported no significant differences in any measure of utilization, symptoms, or lung function. This included the largest of these trials (n=569), the Grampian Asthma Study of Integrated Care. However, as a group, the included trials were underpowered to detect differences in utilization outcomes (such as hospitalization and emergency room visits [which are events that occur infrequently]). Two trials reported statistically significant and striking reductions in emergency room utilization with use of a PFM-based action plan. However, both trials have serious flaws that diminish confidence in the results.

The available evidence does not demonstrate that written asthma action plans improve outcomes. Nor does this evidence refute the hypothesis that use of a written asthma plan is beneficial. If there is benefit in a written asthma

action plan, it is most likely to be found in a population with severe or poorly controlled asthma leading to high utilization of in-hospital and emergency room treatment. As previously stated, two trials reported benefits from a PFM action plan, but neither trial provided a rigorous comparison with a symptom-based plan.

Future Research

The following future research priorities are recommended:

- The overriding priority is to develop a national research agenda for long-term studies to improve the effectiveness of asthma management. Short-term drug efficacy studies are over-represented in the present literature. It is imperative to develop an evidence base that supports clinical decisionmaking on the intensity of treatment, optimization of medication regimens, and utility of disease management interventions for various asthma populations.
- Pediatric studies should have high priority in a national research agenda for long-term studies to improve the effectiveness of asthma management.
- Future asthma trials should use common and internationally accepted definitions for defining asthma severity, other relevant population characteristics, and outcome measures. Distinct definitions for children and adults are likely to be necessary. Validation work is needed on classification schemes for severity. Because classifications of severity and prognosis may evolve with future research, panels of relevant data elements to be collected also should be standardized. The common definitions should include validated instruments for standard measurement of symptoms and quality of life. Finally, compliance with recognized standards for reporting and statistical analyses should be common practice.
- Research to support the rational use of antibiotics should include explicit study questions and populations relevant to the treatment of patients with asthma.

Availability of the Full Report

The full evidence report from which this summary was derived was prepared for AHRQ by the Blue Cross and Blue Shield Association's Technology Evaluation Center under contract number 290-97-0015. Printed copies may be obtained free of charge from the AHRQ Publications Clearinghouse by calling 800-358-9295. Requesters should ask for Evidence Report/Technology Assessment No. 44, *Management of Chronic Asthma* (AHRQ Publication No. 01-E044). When available, Internet users will be able to access the report online through AHRQ's Web site at: www.ahrq.gov.

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