Published in final edited form as:

Expert Rev Clin Pharmacol. 2013 March ; 6(2): 197–219. doi:10.1586/ecp.13.2.

The asthma–chronic obstructive pulmonary disease overlap syndrome: pharmacotherapeutic considerations

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Abstract

Asthma–chronic obstructive pulmonary disease (COPD) overlap syndrome (ACOS) is a commonly encountered yet loosely defined clinical entity. ACOS accounts for approximately 15–25% of the obstructive airway diseases and patients experience worse outcomes compared with asthma or COPD alone. Patients with ACOS have the combined risk factors of smoking and atopy, are generally younger than patients with COPD and experience acute exacerbations with higher frequency and greater severity than lone COPD. Pharmacotherapeutic considerations require an integrated approach, first to identify the relevant clinical phenotype(s), then to determine the best available therapy. The authors discuss the array of existing and emerging classes of drugs that could benefit those with ACOS and share their therapeutic approach. A consensus international definition of ACOS is needed to design prospective, randomized clinical trials to evaluate specific drug interventions on important outcomes such as lung function, acute exacerbations, quality of life and mortality.

Keywords

ACOS; asthma; asthma–COPD overlap syndrome; bronchodilators; chronic obstructive pulmonary disease; corticosteroids; novel therapies; pharmacotherapy

The asthma–chronic obstructive pulmonary disease (COPD) overlap syndrome (ACOS) is poorly recognized in part because clinical trials have consistently ignored this condition, as evidenced by strict inclusion and exclusion criteria that exclude either asthma patients from COPD studies or COPD patients from asthma studies. Asthmatic bronchitis was a term used to describe the overlapping conditions of asthma and COPD by the American Thoracic Society (ATS) in 1962 [1], but no further attempts were made to expound on this clinical phenotype until recently [2–4]. Guidelines from Canada, Japan and Spain attempt to describe this clinical phenotype and establish treatment options [5–7].

Asthma is a syndrome consisting of similar phenotypes with characteristic but nonspecific symptoms. COPD is a syndrome akin to asthma but with important differences, including

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tobacco smoke-induced pathobiology and pulmonary emphysema. An exploration of how best to define ACOS is beyond the scope of this article. However, a clinical definition is a necessary starting point for a review of potential pharmacotherapeutic approaches.

Definition

In clinical practice, separating asthma from COPD is difficult due to the overlapping features common to both diseases. Existing guidelines for asthma, such as the NIH, National Asthma Education and Prevention Program, Expert Panel Report 3 [101], and COPD, such as both GOLD treatment guidelines [102] and the consensus statement by the American College of Physicians, American College of Chest Physicians, ATS and European Respiratory Society [8], also do not fully capture the heterogeneity of asthma and COPD, including ACOS, nor do they prepare clinicians for the variable responses to pharmacotherapies, especially the burden of corticosteroid resistance.

The Spanish COPD guidelines propose four COPD phenotypes that determine differential treatment: nonexacerbator with emphysema or chronic bronchitis, mixed COPD–asthma, exacerbator with emphysema and exacerbator with chronic bronchitis [7].

The mixed COPD–asthma phenotype was defined as an airflow obstruction that is not completely reversible accompanied by symptoms or signs of an increased reversibility of the obstruction [7]. In other guidelines, these patients are described as ‘patients with COPD and prominent asthmatic component’ or as asthma that complicates COPD. Major and minor criteria have been published in a consensus document to define this phenotype [9].

All classification schemes are at best clinical because of the lack of diagnostic laboratory biomarkers and pathology. For the diagnosis, two major criteria ($FEV_1 > 15\%$ and > 400 ml after bronchodilator or sputum eosinophils or history of asthma) and two minor criteria (elevated total IgE or history of atopy or $FEV_1 > 12\%$ and > 200 ml after bronchodilator) are recommended. However, these criteria are neither specific nor sensitive. Airway eosinophilia is not exclusive to asthma and is present in COPD [10], and a clinically significant bronchodilator response ($> 15\%$) can be elicited in the majority of COPD patients [11]. Additional studies are needed to validate and add to these criteria; an international consensus is overdue.

We have previously defined the ACOS as one of two clinical phenotypes from our experience [2]:

- Asthma with partially reversible airflow obstruction – that is, based on change in FEV_1 with bronchodilators – with or without emphysema or reduced carbon monoxide diffusing capacity (DLco) to $< 80\%$ predicted;
- COPD with emphysema accompanied by reversible or partially reversible airflow obstruction, with or without environmental allergies or reduced DLco.

For this review, the authors advocate the following major criteria for ACOS: a physician diagnosis of asthma and COPD in the same patient, history or evidence of atopy, for example, hay fever, elevated total IgE, age 40 years or more, smoking > 10 pack-years,

postbronchodilator $FEV_1 < 80\%$ predicted and $FEV_1/FVC < 70\%$. A 15% increase in FEV_1 or 12% and 200 ml increase in FEV_1 postbronchodilator treatment with albuterol would be a minor criteria.

The similarities and limitations between the Spanish COPD guidelines and our definition for ACOS are apparent. More specific criteria are needed, but the initial screening for ACOS can be achieved with clinical history and pulmonary function tests.

Clinical phenotypes

These two ACOS clinical definitions represent either the hybrid of both eosinophilic bronchiolitis (asthma, typically childhood-onset, Th2-mediated inflammation, induced sputum eosinophilia 3% or more) and neutrophilic bronchiolitis (COPD or adult-onset 'asthma', Th1-mediated inflammation) or independent clinical entities [2]. Both asthma and COPD display variable responses to drug therapies, where COPD is currently the third leading cause of death in the USA [4]. Adults with difficult-to-control (or severe) asthma or COPD that frequently exacerbates (> 2 episodes annually) often fail to improve symptoms or prevent acute exacerbations with treatment recommended by current guidelines and have progressive decline in lung function and quality of life (QoL). ACOS may represent an important population with worse outcomes compared with asthma or COPD alone [2]. Furthermore, exacerbations of greater frequency and severity may occur in ACOS patients despite younger age and a lower burden of cigarette smoking (Table 1) [4].

Recognizing clinical features of disparate obstructive airway disorders and their link with known functional or pathological mechanisms can improve pharmacotherapeutic considerations (Figure 6). New classifications schemes are needed to recognize more specific disease entities or endotypes and their treatment [12,13]. A very recent example of this is asthmatic granulomatosis that presents typically in women with adult-onset severe asthma, low DLco, exhaled nitric oxide level >30 ppb and persistent blood eosinophilia despite treatment with systemic corticosteroids [14].

Phenotype versus endotype

Phenotypes rely on observable characteristics, whereas endotypes relate to underlying functional or pathological mechanisms. Endotypes represent very distinct disease entities, not equivalent to phenotypes, but may cluster in groups of related phenotypes [15]. The clinical course of asthma and COPD syndromes are both punctuated by acute exacerbations, but ACOS may be associated with three times the frequency and severity of exacerbations [4,16]. Whether the three clinical phenotypes of asthma, COPD and ACOS share common endotypes is not yet known. Defining asthma and COPD endotypes is necessary before ACOS can be fully characterized functionally and pathologically.

Prevalence

COPD afflicts 14.2 million adults (a prevalence of one in five) in the USA (emphysema 4.3 million; chronic bronchitis 9.9 million) with an estimated additional 9.8 million people who may have COPD but are undiagnosed (National Health Interview Survey, 2010) [17,18]. Twenty five million Americans (18 million adults and 7 million children) have asthma

(prevalence of 1 in 12 adults) [103]. COPD and asthma are very prevalent in the USA, but the estimates of ACOS prevalence vary depending on how it is defined.

COPD is a deadlier disease than asthma. Nine patients with asthma die each day in the USA [103], whereas one patient with COPD dies every 4 min, or 377 deaths per day. The 30-day mortality for hospitalized severe acute exacerbations of COPD is greater than that of acute myocardial infarction (26 vs 7.8%) [19].

COPD is very prevalent in the younger working-age population, which is contrary to a common perception that COPD affects only elderly patients >65 years old. Approximately 50% of COPD patients, men and women, are younger than 65 years, and they account for two-thirds of total COPD office visits and 43% of all hospitalizations [20].

Women represent 63% of those self-reporting a diagnosis of COPD, and COPD is as common as asthma and diabetes mellitus in the population between the ages of 45 and 64 years [21,22]. Asthma is still considered a disease of younger people, which is reflected in the mean age of enrolled participants in drug trials.

For example, the 1-year GOAL study recruited asthmatics between the ages of 36 and 44 years (despite recruitment criteria for patients between 12 and 80 years) who demonstrated an improvement in FEV₁ of 15% or more (and 200 ml) after inhalation of a short-acting β_2 agonist and had a smoking history of <10 pack-years [23]. By comparison, both the 3-year TORCH [24] and 4-year UPLIFT [25] COPD trials enrolled adults aged 40 years or more with mean ages of 65 ± 8 and 64.5 ± 8 years, respectively, and excluded patients with any history of atopy. These and other studies excluded asthmatics who smoked heavily and those with COPD who are atopic. However, there is a clear overlap in the loss of lung function between severe asthmatics (FEV₁ <60% predicted) and patients with moderate-to-severe COPD (FEV₁ 50–80% predicted and FEV₁ 30–50% predicted).

Consistent with the published literature, and using the above definition, our own clinics have a prevalence of ACOS between 15 and 25% in an adult population of obstructive airway diseases (Figures 1 & 2) [2]. ACOS is also more prevalent in the elderly, African-Americans and among individuals with greater disease severity. ACOS prevalence was even higher in our severe asthma clinics compared with our general pulmonary clinics (24.3 vs 15.8%) (Figures 1 & 2). Among patients referred specifically for difficult-to-control (or severe) asthma, 24.3% had 'concomitant COPD', which best fit our proposed ACOS definition.

Risk factors

COPD is typically not suspected in young smokers aged less than 60 years, and asthma is often not recognized in older patients. Between 15 and 50% of smokers develop COPD [26,27], but a considerable latent period of many years pass before dyspnea becomes the debilitating symptom. Cough and sputum production precede dyspnea, particularly with daily physical activities, such as walking and running.

Important risk factors to consider for ACOS may include cigarette smoking, atopy and possibly age (Figure 6). Cigarette smoking, defined as >10 pack-years, may modify the

small airway inflammation and remodeling associated with bronchial asthma (Box 1). Between 20 and 25% of adult men and women smoke cigarettes in the USA. However, much less is known about the prevalence of smoking in adults with asthma. Based on computed tomography (CT) scanning of the chest, there was no difference in the degree of pulmonary emphysema between those subjects with COPD and those with overlapping features of asthma and COPD [4]. These findings suggest that small airways inflammation rather than emphysematous changes may contribute more to FEV₁ decline in subjects with ACOS. More severe respiratory symptoms, accelerated decline in FEV₁ and an impaired therapeutic response to inhaled corticosteroids (ICS) are consequences of cigarette smoking in patients with asthma [28].

Atopy, the genetic predisposition for the development of an IgE-mediated response to common aeroallergens, is the strongest identifiable predisposing factor for developing allergic asthma. There is no direct evidence that atopy alone causes pulmonary emphysema or the chronic bronchitis typical in COPD. However, α 1-anti-trypsin deficiency in airways may increase the likelihood of developing asthma [29]. COPD patients may manifest allergic symptoms, but it is unknown whether this represents late-onset atopy.

Age is arguably not a risk factor in ACOS. Lung function declines with aging and may confound screening for ACOS. Normal FEV₁/FVC is 0.70 between the ages of 60 and 80 years according to the current NAEPP EPR-3. A FEV₁/FVC <0.70 confirms COPD in the proper clinical circumstances in an adult smoker older than 40 years but should raise the possibility of ACOS in an asthmatic. Adults with asthma, especially if they are smokers, lose FEV₁ more rapidly than nonsmoking asthmatics [30]. The influence of aging alone in the progression of asthma or COPD remains a controversial topic [31]. In our experience, patients with asthma tend to be younger (mean age: 51.3 years) than those with ACOS, and those with COPD tend to be older (mean age: 72.4 years) than those with ACOS (mean age: 66.7 years) [2].

A recent cross-sectional study of subjects with COPD and asthma overlap enrolled in the COPDGene™ project highlight the aforementioned risk factors relevant to ACOS. Asthma was found in 13% (119 out of 915) of those with COPD, identified by physician-diagnosed asthma before the age of 40 years [4]. There was no predilection for either gender, but there was a preponderance of African-Americans in the study's overlap group. These patients were younger (61.3 vs 64.7 years; $p = 0.0001$) with fewer pack-years of cigarette smoking (43.7 vs 55.1 pack-years) compared with patients with COPD alone (i.e., COPD without asthma), a finding comparable to our experience. The GOLD stage distribution was remarkably matched; for example, 51.3% in both the groups with moderate stage (grade) II and 31% with severe stage (grade) III COPD. Overlap patients had more evidence of air trapping on chest CT than those with COPD. There was no difference in spirometry or CT measurements of pulmonary emphysema or airway wall thickness, but overlap patients were more likely to have significantly worse QoL and more frequent acute exacerbations than patients with lone COPD (Figure 3) [4].

Expert commentary

The Spanish COPD guidelines recommend treatment of the mixed COPD–asthma phenotype with ICS and a long-acting bronchodilator (LABD) as a first option to improve lung function, respiratory symptoms and to reduce exacerbations. With greater clinical severity, they recommend adding a long-acting muscarinic receptor antagonists (LAMA) to ICS + long-acting β_2 agonist (LABA) combination for ‘triple therapy’. In even more severe cases, theophylline or roflumilast may be added [7]. This review will elaborate upon these recommendations and review pharmacotherapeutic considerations in asthma, COPD and ACOS.

Principles of treatment

- Cost-effective symptom control and reducing acute exacerbations without causing major adverse events;
- Safe and well-tolerated when added to the usual combination treatments without diminishing effectiveness;
- Affordable and available, similar to other prescription drug treatments for asthma and COPD;
- Evidence-based and mitigates the risk and functional impairment from asthma and/or COPD; for example, reducing acute exacerbations and improving symptoms;
- Uses controllers or maintenance medications that control symptoms and prevent acute exacerbations and hospitalizations;
- Demonstrates beneficial anti-inflammatory effects without compromising innate immunity or host defense;
- Provides a clinically meaningful increase in health-related QoL as measured by validated survey instruments (e.g., St George’s Respiratory Questionnaire or Asthma Control Test or COPD Assessment Test);
- Requires no more than twice-a-day dosing with effective delivery devices that are simple for patients to use.

The goals of treatment in ACOS should be to control or reduce symptoms and impairment and to reduce risks, including acute exacerbations, decline in lung function and adverse effects from drug treatments (Figures 4 & 5). Morbidity from ACOS can result from coughing, wheezing, sputum production, dyspnea on exertion, physical deconditioning and adverse effects from drug treatments. Mortality can result from frequent exacerbations and complications, including acute respiratory failure.

The objectives or the steps needed to reduce risk and to reduce impairment should be attainable (within timeline of 3 months), measurable (e.g., control questionnaire scores, FEV₁, exhaled nitric oxide [eNO]), and cost effective (e.g., number needed to treat [NNT], acceptable risk of adverse drug effects), as should the objectives for preventing exacerbations (Table 2 & Figure 5).

Narrow- versus broad-spectrum drugs

Utilitarian language to link drug treatment to the three syndromes including asthma, COPD and ACOS is discussed. Drugs for the treatment of these three syndromes can be considered narrow spectrum – that is, specific for asthma or COPD only – or broad spectrum – that is, effective for both asthma and COPD (Figure 6). Examples of narrow-spectrum drugs include the leukotriene receptor antagonists (LTRAs) and monoclonal antibodies, such as omalizumab, for the treatment of asthma. Broad-spectrum drugs may include bronchodilators, corticosteroids, theophylline and antibiotics, which have ‘dual efficacy’ and can treat both asthma and COPD.

Important primary outcome measures

The rate of exacerbations should be a primary outcome and ultimate target of drug treatment. Acute exacerbations when frequent may increase patient morbidity, mortality and certainly the economic and social burden of disease. Between 50 and 75% of COPD healthcare costs in the USA are due to the treatment and management of acute exacerbations [104]. The typical patient with severe to very severe COPD will average at least two or more exacerbations annually, whereas patients with ACOS can experience significantly more exacerbations each year, up to 2 or 2.5 times as many as those with lone COPD (Figure 3) [4]. Similarly, the controlled asthmatic will experience two or more exacerbations annually [101].

Targets of treatment

It is important to try and target treatments to disrupt pathobiologic processes that give rise to pathophysiologic patterns in asthma, COPD and ACOS. Small airway inflammation and smooth muscle dysfunction (Figure 4) are not the only targets of treatment in asthma and COPD. Mucociliary dysfunction, chronic infections with advancing immunosenescence and pulmonary emphysema as seen in COPD may be just as relevant to ACOS. Possible drug targets include receptors of the parasympathetic and sympathetic nervous systems that terminate in the tracheobronchial tree; hypertrophied bronchial smooth muscles; the complex cytokine network activated by infections; and cellular and humoral processes, among others that contribute to airways inflammation and smooth muscle bronchoconstriction. On the basis of this simplified understanding, pharmacotherapeutics can attempt to disrupt relevant pathobiologic mechanisms or underlying etiologic factors, including:

- Tobacco smoking;
- Th2-mediated pathways and inflammation, such as CD4⁺ lymphocytes, mast cells, eosinophils, neutrophils, epithelial cell remodeling with goblet cell hyperplasia, IgE, IL-13 and IL-5 in asthma;
- Th1-mediated pathways and inflammation, such as CD8⁺ and CD4⁺ lymphocytes, alveolar macrophages, neutrophils, eosinophils, epithelial cell remodeling, IFN- γ in COPD;
- Mucus hypersecretion, goblet cell hyperplasia;

- Smooth muscle hypertrophy and dysfunction;
- Airway angiogenesis;
- Airway fibrosis and subepithelial basement membrane thickening;
- Pulmonary emphysema;
- Acute and chronic infection; for example, viral, bacterial, fungal colonization, and so on.

Endotyping clinical phenotypes based on pathobiology and response to medications can personalize drug therapies for patients, avoid unwarranted treatments and possibly reduce need for other drugs, such as oral corticosteroids. An example of specific endotyping in current clinical practice is the steps required to identify patients with difficult-to-control/severe asthma who qualify for omalizumab injections. This is performed in part by demonstrating elevated total IgE levels within a predefined range (30–700 IU/ml) and IgE antibodies to perennial environmental allergens.

Five-year view

Current drug classes

Current drug treatments have been incorporated into clinical practice guidelines, such as the NAEPP EPR-3 for asthma [101] and GOLD treatment guidelines for COPD [102], both of which recognize the enduring risk of acute exacerbations. Knowledge of these treatment guidelines is important to help patients achieve basic control of their disease. The value of emerging peer-reviewed, large, randomized clinical trials and meta-analyses is that they add to current therapeutic strategies [32]. Clinical trials that enroll patients from the ‘real world’, instead of professional study subjects, are of greater value because they more closely reflect actual clinical practice.

Current controller drugs for asthma include ICS, LABA, LTRA, omalizumab and theophylline. Current rescue drugs for asthma include short-acting β_2 agonists (SABA), short-acting muscarinic antagonists (SAMA), systemic corticosteroids and in some cases, antibiotics.

Current maintenance or controller treatments for COPD include tiotropium, LAMA, LABA, LABA + ICS, LAMA + LABA, roflumilast, theophylline, and ‘triple therapy’ combining LAMA + LABA + ICS. Current rescue drugs for COPD include SABA, SAMA, systemic corticosteroids and antibiotics.

Box 2 summarizes the current and emerging drug therapies for asthma and COPD, with possible application to ACOS. Table 2 summarizes the influence of current drug treatments on acute asthma or COPD exacerbations, listing recent clinical trials and meta-analyses with the NNT to prevent one exacerbation. Of particular note is the impact of COPD patient education and self-management, which registered the lowest NNT (NNT = 2 to prevent one COPD hospitalization) [33].

Smoking cessation

Smoking cessation is the most important and only proven disease-modifying intervention in COPD, which also reduces all-cause mortality. However, there are still patients who progressively lose lung function and become disabled from COPD and ACOS, even after smoking cessation [34]. Women former smokers may have a more rapid decline in FEV₁ than lifetime nonsmokers, but men who formerly smoked had a slower rate of FEV₁ decline than lifetime nonsmokers, a paradoxical observation not explained in longitudinal studies [35].

Patients with asthma, COPD and ACOS should always be encouraged to stop smoking, despite the low, sustained abstinence rates (ranging from 15 to 25%). Although 75% of smokers want to stop smoking, <5% of those attempting to quit (without education and pharmacological aids) are successful [36]. Active cigarette smoking enhances symptom severity in asthma, accelerates the decline in lung function and impairs short-term therapeutic responses to ICS. The mechanisms of ICS resistance in smokers with asthma are not fully explained but could be a result of alterations in airway inflammatory cell phenotypes, for example, increased neutrophils or reduced eosinophils, changes in the glucocorticoid receptor- α to - β ratio (e.g., overexpression of glucocorticoid receptor- β) and/or increased activation of proinflammatory transcription factors such as NF- κ B or reduced histone deacetylase activity [28].

The pharmacotherapy for smoking cessation consists of first-line agents approved by the US FDA as aids to quitting attempts. These include nicotine replacement therapy (NRT) in the form of a patch, gum, lozenge (all available without prescription), spray and/or inhaler; and non-nicotine medications such as bupropion and varenicline [37,38]. One-year abstinence rates approach 15% with bupropion and 24% with varenicline.

Combining different forms of NRT or simultaneously administering NRT and non-nicotine medications can increase smoking abstinence rates. Newer treatments such as varenicline target α_4 , β_2 -nicotinic acetylcholine receptors in the mesolimbic nervous system and thereby block nicotine from binding to these receptors.

The nicotine vaccine produces nicotine-specific antibodies that bind to nicotine from tobacco smoking, creating a large complex that cannot cross the blood–brain barrier to bind α_4 , β_2 -nicotinic acetylcholine receptors.

Two recent, large Phase III clinical trials with a conjugated nicotine vaccine failed to achieve significant abstinence rates [39]. Vaccine potency may be improved by introducing novel carriers and/or adjuvants to stimulate the proper immune responses needed to maintain abstinence and prevent relapse. Unfortunately, at least half of smokers relapse within a year of smoking cessation [35,36].

Narrow- versus broad-spectrum drugs

Bronchodilators SABA & SAMA

Used primarily for rescue in asthma but may be used for control/maintenance in

COPD: Inhaled SABA are the most widely used treatment for acute relief of asthma and

COPD symptoms. Consensus guidelines now generally recommend using SABAs only for acute relief of symptoms on an ‘as needed’ basis. Meta-analyses of numerous studies support current NAEPP EPR-3 treatment guidelines regarding SABA use. Evidence is reassuring against concerns over the regular use of SABA and the incidence of exacerbations, when regular treatment was compared with ‘as needed’ treatment [40]. The use and need for SABA treatments sustained over 2–3 days without relief of symptoms may foreshadow an acute exacerbation of asthma, COPD or ACOS. The number needed to harm over 6 months is 200 patients with asthma and/or COPD, primarily from cardiac tachyarrhythmias and hypokalemia [41].

Inhaled anticholinergic agents or SAMA such as ipratropium are used in the treatment of COPD more than in asthma. They induce bronchodilation by blocking muscarinic receptors M_1 and M_3 in the airways and bronchial smooth muscles.

A meta-analysis of studies comparing a combination of SAMA + SABA versus SABA alone in asthmatics showed no significant differences between the two regimens with respect to symptom scores or peak flow rates [42]. Asthma should be controlled with anti-inflammatory medications such as ICS, the cornerstone of asthma drug treatment. However, this does not preclude the possibility that there may be a subgroup of patients who derive benefit from SAMAs and a trial of treatment in individual patients may be justified. The parasympathetic nervous system may contribute more to bronchospasm in those with asthma who smoke cigarettes. The role of LAMA such as tiotropium bromide has only recently been established in those with asthma [43], whereas in COPD, it is a first-line LABD.

Long-acting β_2 agonists—Current benefits from inhaled LABA such as salmeterol and formoterol in the treatment of asthma continue to outweigh risks, which include a FDA ‘black box’ warning contraindicating their monotherapy, and warning their use causes asthma deaths either alone or in combination with other medications. LABAs remained the preferred add-on drug to ICS in the NAEPP EPR-3. LABAs have been replaced recently by LAMAs as first-line bronchodilators for use in COPD in the most current GOLD guidelines.

The FDA recommend LABAs be added to ICS in a fixed combination (ICS + LABA) for the shortest time needed to achieve asthma control. The LABA is then to be discontinued, leaving patients on ICS as their controller agent [44]. No clinical trials are available to guide step-down decisions in these patients who have moderate-to-severe persistent asthma. The current NAEPP-EPR-3 does not recommend stopping LABA first; instead they recommend reducing the dose of ICS prior to discontinuing LABA.

The LABAs are not anti-inflammatory drugs, but they can significantly reduce asthma exacerbations as well as the rate of COPD exacerbations compared with placebo irrespective of COPD severity, smoking history or duration of COPD [45]. LABAs are important bronchodilators in COPD, and their discontinuation in patients with ACOS is difficult to recommend because the risk of acute COPD exacerbations is much greater than the risk of asthma-related deaths [46].

Every patient, regardless of whether they have asthma, COPD or ACOS, should be encouraged to report any deterioration, for example, worsening of cough, wheezing and dyspnea, following initiation of LABA treatment to promote safety. A recent meta-analysis of five randomized controlled trials where adolescent and adult asthmatics either discontinued LABA therapy or continued LABA therapy after achieving control with ICS + LABA was supported by the ATS, the American Academy of Allergy, Asthma and Immunology and McMaster University (Ontario, Canada) to discern whether withdrawing LABA worsened asthma control achieved with combination ICS + LABA as recommended by the FDA. LABA discontinuation was associated with a drop in QoL score, 9.2% fewer symptom-free days and an average of 0.71 more puffs per day from a rescue bronchodilator [47].

The POET study investigated which LABD inhaler, LABA versus LAMA, to consider initiating first in patients with moderate-to-severe COPD and a history of exacerbations [48]. The trial enrolled 7376 COPD patients and demonstrated that tiotropium significantly delayed the occurrence of the first COPD exacerbation, a significant 17% overall risk reduction compared with salmeterol. However, the combination of LABA + LAMA in COPD also provides an additive benefit, producing greater symptom control and improvement in FEV₁ than either drug alone [49].

Extrapolation of the POET study to individuals with ACOS is complicated by the fact that patients were allowed to continue treatment with ICS during the study. Use of ICS at baseline was evenly distributed between the groups but does not appear to have been taken into account during randomization. The ideal subgroup analysis of the POET study data would be tiotropium versus salmeterol (with no ICS use in either group) in patients with FEV₁ 50% predicted or greater, and tiotropium versus salmeterol + ICS in people with FEV₁ <50% predicted.

Long-acting muscarinic antagonists—LAMA are potent and first-line bronchodilators in COPD but generally take longer to have effect than their LABA bronchodilator counterparts. Tiotropium and aclidinium are currently available for prescription.

Tiotropium is a once-daily inhaled ultra-LAMA for COPD that works through prolonged blockade of the M₃ muscarinic receptor. The half-life for tiotropium is 36 h compared with SAMA and SABA of approximately 26–30 min.

Tiotropium significantly reduces the risk of acute COPD exacerbations, effectively controls symptoms such as dyspnea, and improves exercise tolerance in COPD as maintenance treatment ranging from 1 to 4 years [25,50]. It is effective when added to usual care including ICS, LABA and theophylline with a NNT of 8 to prevent one exacerbation per year in GOLD Grade II through GOLD Grade IV, and a NNT of 7 in GOLD Grade II. However, tiotropium in the 4-year UPLIFT study did not affect the annual decline in FEV₁ across GOLD grades.

The TALC study, a three-way, double-blind, triple-dummy crossover trial, was conducted to evaluate the addition of tiotropium to ICS, compared with a doubling of the ICS dose or the

addition of the LABA salmeterol in 210 asthmatics over a 52-week study period [43]. Tiotropium produced superior morning peak expiratory flows, number of asthma control days, prebronchodilator FEV₁ and daily symptom scores when compared with a doubling of the ICS dose. The addition of tiotropium was not inferior to the addition of salmeterol for all assessed outcomes but significantly increased prebronchodilator FEV₁ more than salmeterol, with a difference of 110 ml.

When added to ICS, tiotropium improved symptoms and lung function in patients with inadequately controlled asthma. Its effects appeared to be equivalent to those with the addition of salmeterol [43]. The implications of these results for ACOS are important since LAMAs are not recommended in the current NAEPP EPR-3. Available guidelines invariably lag behind pharmacotherapeutic advances in recently published literature.

Tiotropium was found to be effective in improving FEV₁ and need for albuterol in COPD patients with concomitant asthma in a recent clinical trial [51]. In this study, 472 COPD patients were randomized to either tiotropium or placebo for 12 weeks and permitted to continue all prescribed medications except for inhaled anticholinergics. Spirometry was measured serially for 6 h on days 1, 29 and 85. Baseline characteristics were similar between groups: a mean age of 59.6 years, 61.4% were men, and FEV₁ was 53% predicted. Statistically significant improvements at 12 weeks with tiotropium were observed for the primary end point FEV₁ area under the curve (AUC) from 0 to 6 h and for morning predose FEV₁. Significant increases in FVC were found in the tiotropium group compared with placebo [51].

The addition of tiotropium in two replicate 48-week, randomized, controlled PrimoTinA-asthma trials involving 912 asthmatics with persistently abnormal lung function (FEV₁ 80% predicted) and at least one severe exacerbation in the previous year despite the use of ICS + LABA significantly increased the time to the first or next severe exacerbation and provided modest sustained bronchodilation. The time to the first severe exacerbation increased from 226 days in the control group to 282 days with tiotropium added, a significant overall reduction of 21% in risk [52]. Meta-analysis of nine COPD trials where tiotropium was added to usual care COPD treatments found tiotropium reduced acute exacerbations, hospitalizations, improved QoL and symptoms [53].

Acclidinium is a new inhaled long-acting M₃ receptor antagonist taken twice daily and, unlike tiotropium, it is rapidly metabolized by ester hydrolysis in plasma into its alcohol derivatives, reducing systemic anticholinergic adverse effects, for example, dry mouth and urinary retention, to <1%. It may also improve nocturnal symptoms when compared with once-daily tiotropium [54].

Newer inhalers such as the once or twice-daily LAMA + LABA combinations, for example, aclidinium + formoterol, umeclidinium + once-daily vilanterol and tiotropium + olodaterol, will advance and broaden the available formulary for COPD and possibly ACOS. The inhaler combining the ultra-LABA indacaterol and the ultra-LAMA glycopyrronium increases FEV₁ by a mean of 300 ml, well above the minimal clinically important difference (MCID) of 100 ml [55].

Inhaled corticosteroids—ICS are the most effective anti-inflammatory drugs in the management of asthma syndromes. Inhaled and systemic corticosteroids affect mainly Th2-type lymphocytes and their response to allergen triggers and viral infections. Excellent reviews of the mechanism of action of corticosteroids have been published [56]. All ICS differ in potency by weight but are equivalent in efficacy if enough is used, albeit at the risk of causing significant adverse side effects (Box 2). At present, triamcinolone is the least potent ICS and fluticasone furoate is the most potent. Corticosteroids bind to cytoplasmic glucocorticoid receptors that translocate to the nucleus of airway and mucosal inflammatory cells to reverse histone acetylation, which is essential for the transcription of proinflammatory genes. Increasing levels of the nuclear enzyme histone deacetylase-2 is the proposed effect of corticosteroids.

ICS can prevent asthma deaths but they are not disease modifying in that the natural course of persistent asthma is not altered [101] in the manner smoking cessation can arrest the accelerated annual decline of lung function as measured by FEV₁. Oral corticosteroids are used to treat acute exacerbations of asthma and status asthmaticus. They may be used as a controller agent in patients with severe-persistent asthma that is not controlled by step 5 treatments in NAEPP EPR-3 treatment guidelines [101].

Conversely, ICS use is controversial in COPD and only the medium doses of ICS in fixed combinations ICS + LABA inhalers are FDA-approved to control symptoms and reduce acute exacerbations – that is, fluticasone propionate 250 µg + salmeterol 50 µg in a Diskus® one inhalation twice daily or budesonide 160 µg + 4.5 µg formoterol two puffs twice daily in a metered dose inhaler. The NNT with fluticasone (either 250 or 500 µg) + salmeterol in a Diskus was 2 to reduce one exacerbation a year (Table 2) [57,58]. By comparison, the NNT was 8 for the highest dose of fluticasone propionate 500 µg + salmeterol versus placebo, and in the 3-year TORCH study, the NNT was 8 versus salmeterol. Both ATS and ERS recommend ICS be added to a LABD (LABA or LAMA) if the FEV₁ <50% predicted or if the patient has experienced an acute exacerbation in the past year [59].

In the GOAL study [23], increasing the ICS dose in ICS + LABA combinations (fluticasone propionate + salmeterol) for 1-year duration improved asthma control, which included a short oral corticosteroid trial. However, 30% of patients did not achieve adequate asthma control. This group, although ‘nonsmokers’ (as defined by a smoking history <10 pack-years), could have unrecognized elements of COPD and thereby meet the clinical definition of ACOS.

Use of ICS in COPD and possibly ACOS should balance the potential benefits (e.g., reduced asthma deaths, reduction in exacerbations and decline in QoL), against the known increase in adverse effects (e.g., oropharyngeal candidiasis, vocal hoarseness, viral infections). Current evidence supports existing treatment guidelines advocating LABDs (LAMA, LABA) as first-line therapy for COPD, with regular ICS therapy as an adjunct in COPD patients experiencing frequent exacerbations. ICS do not improve lung function in COPD, but they may be added to LABA and/or LAMA primarily to prevent acute exacerbations of COPD.

Triple therapy—Patients with obstructive lung disease who have frequent exacerbations (> 2 per year) or have a $FEV_1 < 50\%$ predicted may benefit from all three drugs or ‘triple therapy’: ICS, LABA and LAMA. Combinations of LABA + LAMA + ICS in separate inhalers are used in patients with asthma and COPD to improve and control symptoms and to reduce exacerbations. The 4-year UPLIFT study provides the most convincing evidence that triple therapy is effective in controlling symptoms and preventing acute COPD exacerbations. However, the effectiveness in each of the three syndromes, including ACOS, is difficult to establish from these data alone.

Despite recommendations from GOLD and the ACP/ACCP/ATS/ERS consensus statement to use ICS in COPD, several authorities remain unconvinced that ICS are effective and recommend only LAMA + LABA combination bronchodilator therapy. Based on our experience, COPD patients with asthma or the ACOS may benefit from a single inhaler combining ICS + LAMA + LABA, while recognizing that corticosteroid resistance may play a role in both COPD and ACOS from tobacco smoking. Moreover, based on the PRICE study, 46% of nonsmoking subjects with asthma display ICS resistance [60], further complicating how patients with ACOS would respond to ICS or triple therapy.

Narrow-spectrum agents for asthma & ACOS

Leukotriene modifiers

Leukotriene receptor antagonists: NAEPP EPR-3 recommends ICS as first-line controller therapy primarily because of their well-established efficacy in clinical trials. Until recently, LTRA have not been considered first-line treatment except in the pediatric population. Leukotrienes are potent mediators of inflammation once known as slowly reactive substances of anaphylaxis. Inhaled and oral corticosteroids do not inhibit leukotriene production or affect their urinary excretion. A favorable response to LTRAs, as an empiric trial, may detect leukotriene-driven inflammation in those with COPD or ACOS.

Two ‘real-world’ clinical trials evaluated LTRA as first-line monotherapy or as add-on therapy to ICS for the treatment of persistent asthma in adult patients [61]. Patients were randomly assigned to 2 years of open-label therapy with LTRA alone or LTRA + ICS versus ICS alone or ICS + LABA. QoL improved in all treatment groups and in 2 months met predefined definition of equivalence in both monotherapy and add-on trials. Equivalence between the groups was approached but not achieved at 2 years. Most importantly, the rate of exacerbations and level of asthma control did not differ between the treatment groups during the trials. Adherence was greater in the LTRA groups versus the ICS groups. The investigators concluded LTRA can be considered equivalent to both ICS as first-line controller therapy and to LABA as add-on therapy in ‘real-world’ practice. The NAEPP EPR-3 treatment guidelines list the addition of a LTRA to ICS as an alternative to the preferred treatment of adding a LABA to ICS. By these guidelines, last updated in 2007, adding a LABA to ICS is preferred to adding LTRA to ICS in the drug treatment of asthma.

At present, there is no clear data for adding LTRA to a fixed-dose combination of ICS + LABA. An open-labeled study evaluating the efficacy of montelukast in improving asthma control in patients not controlled on fixed moderate dose of ICS + LABA found nearly 80%

of patients treated with montelukast reported global improvement in their asthma control [62]. Leukotriene modifiers should not be prescribed routinely in COPD unless asthma or ACOS is suspected and not continued unless a favorable clinical response is achieved.

5-lipoxygenase inhibitors—Leukotriene-mediated inflammation has been implicated in COPD exacerbations but neither montelukast (a LTRA) nor zileuton (an oral 5-lipoxygenase inhibitor) have been effective in reducing COPD exacerbations. A randomized, double-blind, placebo-controlled, parallel group study of zileuton versus placebo for 14 days starting within 12 h of hospital admission for COPD exacerbation, failed to shorten hospital stay despite a drop in urinary leukotriene E₄ levels in the zileuton-treated group as compared with placebo at 24 h [63].

Zileuton is an option in treating mild-to-moderate asthma but has been used anecdotally to treat severe asthma based on bronchoscopic evidence of increased neutrophilic inflammation in severe, corticosteroid-dependent asthma [64]. Although production of leukotrienes LTB₄, LTC₄, LTD₄ and LTE₄ is partially inhibited, zileuton should not be prescribed in adults with asthma before ICS, LABA, LTRA have been tried. Zileuton remains in the current NAEPP EPR-3 treatment guidelines by panel consensus judgment, the weakest recommendation and not through randomized, controlled clinical trials. Monitoring liver enzyme elevation (1.8% of patients on zileuton vs 0.7% in placebo-treated patients) is required for the first 3 months of treatment and every 2–3 months afterwards for the remainder of the first year and periodically thereafter. The majority of liver enzyme elevations resolved within 3 weeks after discontinuation.

Omalizumab—Omalizumab is a recombinant DNA-derived humanized monoclonal murine antibody that selectively binds to free IgE in blood, thereby reducing binding of IgE to mast cells and basophils. It is an important endotype-specific treatment of difficult-to-control asthma that is recommended by the current NAEPP EPR-3 before daily prednisone use or with prednisone use [65]. Omalizumab is approved for subcutaneous injection in adults and adolescents (aged 12 years and older) with moderate-to-severe persistent asthma who have a total IgE between 30 and 700 IU/ml, positive skin test or *in vitro* reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with ICS or prednisone. Omalizumab is effective in controlling asthma symptoms and preventing acute exacerbations with a NNT of 10 in a recent meta-analysis [66]. A relationship between the risk of asthma and serum IgE levels has been observed and approximately 60% of those with asthma have evidence of atopy [67]. There are no studies of the efficacy of omalizumab in ACOS. Nine out of 26 patients who met the aforementioned definition of ACOS in our severe asthma clinics responded well to omalizumab with a reduction in exacerbation rate and need for prednisone. Therefore, in selected patients with ACOS, this treatment may have benefit; however, clinical trials are needed to confirm this observation.

Indications are restrictive and reflect the inclusion criteria of the INNOVATE trial, which enrolled individuals with asthma taking high-dose ICS + LABA and additional controller medications [68]. Smokers or those with a smoking history of ≥ 10 pack-years were excluded from the INNOVATE study. Add-on omalizumab in the INNOVATE trial significantly reduced exacerbation rates by 26% (NNT = 3), severe exacerbation rates by 50% (NNT = 2),

emergency visit rates by 44% (NNT = 3) and significantly improved asthma-related QoL compared with placebo.

The ACOS patient with elevated IgE levels may warrant alternative treatments (e.g., tiotropium, roflumilast, and so on) prior to a 4–6-month trial of omalizumab, to control symptoms and prevent acute exacerbations. Drug costs and strict requirements surrounding omalizumab prescription limit the use to asthma patients with greater likelihood of treatment response. Between 4 and 6 months, omalizumab use should be reviewed and treatment discontinued if there is no improvement in asthma control. There are no studies that have evaluated omalizumab in smokers or those with smoking history; hence, the benefit of omalizumab in COPD or ACOS remains an open question.

Broad-spectrum for all three syndromes

Combinations of ICS ± LABA ± LAMA ± LTRA ± omalizumab—To compare the efficacy and safety of ICS, LABAs, tiotropium, LTRA, omalizumab and combination products for patients with persistent asthma, Jonas *et al.* searched MEDLINE, the Cochrane Library, Embase, International Pharmaceutical Abstracts, and reference lists for published clinical studies through September 2010 [69]. Their findings provide a valuable perspective that validated NAEPP EPR-3 treatment guidelines that may have bearing on ACOS. Efficacy studies provided moderate strength of evidence that equipotent doses of ICS administered through comparable delivery devices do not differ in their ability to control asthma symptoms, prevent exacerbations, reduce the need for additional rescue medication or in their overall incidence of adverse events or withdrawals due to adverse events. There was no difference between montelukast and zafirlukast in their ability to decrease rescue drug use or improve QoL; between formoterol and salmeterol in their ability to control symptoms, prevent exacerbations, improve QoL or cause harm among patients not controlled on ICSs alone; or between budesonide + formoterol and fluticasone + salmeterol combinations for efficacy or harm when each combination is administered through a single inhaler. There was greater benefit for subjects treated with ICS monotherapy compared with those treated with LTRA monotherapy. Direct evidence suggested no difference in tolerability or overall adverse events between ICSs and LTRA. Specific adverse events reported with ICS, such as cataracts and decreased growth velocity, were not found among patients taking LTRA. The data indicated that ICS and LTRA are safer than LABA used as monotherapy. Indirect evidence suggested that the increased risk of asthma-related death in those taking LABA may be confined to patients not taking ICS at baseline. There was no evidence to support the routine use of combination therapy rather than an ICS alone as first-line therapy. With respect to combinations of inhalers with omalizumab, the published literature is restricted to the above discussion on omalizumab.

In this same meta-analysis, results from several large trials supported greater efficacy with the addition of a LABA to an ICS than with a higher dose ICS, and greater efficacy with the addition of a LABA to an ICS over continuing the current dose of ICS alone for poorly controlled persistent asthma [69]. The addition of LTRA to ICS compared to continuing the same dose of ICS resulted in improvement in rescue albuterol use and no statistically significant differences in other health outcomes. There was no apparent difference in

symptoms, exacerbations, rescue medicine use, overall adverse events or withdrawals due to adverse events between those treated with ICS + LTRA compared with those treated with increasing the ICS dose. No difference was found in overall adverse events or withdrawals due to adverse events between ICS + LABA and ICS + LTRA.

Overall, there was no evidence that any one drug for asthma within any of the classes evaluated was significantly more effective or harmful than the other medications within the same class, with the exception of zileuton being more harmful than the other leukotriene modifiers. This analysis of patients with persistent asthma supported the general clinical practice of starting treatment with an ICS. For patients with poorly controlled, persistent asthma taking an ICS, the addition of a LABA provides the greatest benefit. Limitations of this review as well as NAEPP EPR-3 include the younger age of study subjects, the absence of significant cigarette smoking and the limited duration of the reported clinical trials.

The 4-year UPLIFT trial strongly supports the use of combination therapy or triple therapy with LAMA + LABA ± ICS in COPD with a 14% reduction in acute exacerbations, sustained improvement in FEV₁ and a reduction in the risk of all-cause mortality including cardiovascular death despite no effect on the annual rate of decline in FEV₁. Sixty two percent of the study patients continued their ICS treatments previously prescribed and 60% of patients also continued LABAs.

If asthma features evident in a COPD patient, we recommend following NAEPP EPR-3 and trialing first with an ICS (preferred) or LTRA (alternative) to treat airway inflammation. These COPD patients will probably be treated with one or two long-acting bronchodilators (LAMA or LABA or both) to provide sustained bronchodilation, reduce symptoms and prevent acute exacerbations. If chronic bronchitis from cigarette smoking or COPD is suspected in an asthmatic, then beginning treatment with a LAMA is preferable as outlined by the GOLD treatment guidelines for COPD. Measurement of FeNO (normal < 25ppb) or induced sputum eosinophil counts may discover inflammation secondary to eosinophils and help decide whether a trial of ICS or LTRA is warranted in a COPD patient.

PDE4 inhibitors

Roflumilast: Roflumilast is the only oral phosphodiesterase-4 (PDE4) inhibitor currently available to treat COPD by reducing the risk of acute exacerbations. PDE4 is one of at least ten different esterases known to catalyze the breakdown of intracellular cyclic adenosine monophosphate (cAMP). The accumulation of intracellular cAMP is thought to attenuate the activation of inflammatory cells and cytokine release *in vitro*. Roflumilast has been reported to reduce sputum eosinophils and neutrophils by 42 and 31%, respectively, in a small study of COPD patients. The significance of these findings is unknown, but the potential dual benefit of roflumilast in asthma and ACOS is currently under clinical investigation. At present, it is approved in the USA and Europe for COPD patients with GOLD Grade III or IV and a history of exacerbations and chronic bronchitis in adults aged 40–65 years or older. Roflumilast significantly reduced the rate of moderate-to-severe acute exacerbations versus placebo in patients using concomitant LABA, SABA or SAMA in two large 1-year pivotal trials [70]. The use of ICS, tiotropium and theophylline was not allowed during the pivotal trials. A combined and significant 17% reduction in moderate-to-severe acute exacerbations

was achieved [71]. The NNT was 3.64 to prevent one exacerbation per year in one study and 5.29 in the other, combined to give a NNT of 4. A subsequent *post-hoc*, pooled analysis of 2686 randomized COPD patients in whom concurrent use of ICS was permitted demonstrated a significant 14.3% decrease in exacerbations compared with placebo [72]. There are no direct comparison studies against ICS in COPD patients as an alternative add-on therapy to LABDs.

Roflumilast improved FEV₁ by 48 ml in COPD patients, but this did not reach the minimal clinically important difference of 100 ml to meet the definition of a bronchodilator. This drug should never be used for the relief of acute bronchospasm. Roflumilast is contraindicated in COPD patients with moderate-to-severe liver disease (Child–Pugh class B or C). The most common adverse effect associated with roflumilast is diarrhea (9.5%), weight loss (7.5%), nausea (4.7%) and headache (4.4%).

Methylxanthines

Theophylline: Theophylline is perhaps the least understood drug in the treatment of asthma and COPD [73]. Theophylline is available in immediate and sustained-release formulations. Although indicated for the treatment of asthma and COPD symptoms, it has fallen out of favor and is currently a third-line controller/maintenance drug per the NAEPP EPR-3 and GOLD treatment guidelines. Theophylline has been ascribed with various therapeutic effects as a nonselective PDE inhibitor, ranging from a placebo to a bronchodilator, an adenosine receptor antagonist, and a mucoregulator. Intracellular levels of cAMP increase through the inhibition of PDE4, PDE3 and for cyclic guanosine monophosphate by the inhibition of PDE5. Mucociliary clearance is enhanced by ciliary beat frequency and water transport. In addition to bronchodilator and anti-inflammatory effects, theophylline can induce apoptosis of neutrophils and eosinophils, and affect immunomodulation by releasing IL-10 from alveolar macrophages.

Theophylline is associated with a reduction of COPD exacerbations but was less effective than ICS in COPD patients with frequent exacerbations [74]. There was an 11% reduction in the risk of moderate-to-severe exacerbations in theophylline versus LABA users (NNT = 9). There was a 22% reduction in moderate-to-severe exacerbations in ICS versus theophylline users (NNT = 4.5), which supports current GOLD treatment guidelines.

Anti-inflammatory effects are seen with serum theophylline levels <10 mg/l. A higher range of 10–20 mg/l is necessary for bronchodilator effects, but toxic adverse effects become apparent. Theophylline blocks the adenosine A2b receptor, preventing histamine and leukotriene release from mast cells. The degree of PDE4 inhibition, the presumed primary mechanism of action, is very small at levels <10 mg/l.

Theophylline at serum levels of <5 mg/l can selectively restore histone deacetylase to reduce histone acetylation at activated inflammatory gene promoters within inflammatory cell nuclei [75]. This also downregulates the generation of proinflammatory transcription factors, such as NF- κ B. It has been proposed that theophylline can reverse corticosteroid resistance in patients with COPD. In ACOS, those who smoke may benefit; however, clinical trials are lacking to confirm that acute exacerbations can be reduced through this specific mechanism.

Alternative treatments

Mucolytics & azithromycin: Carbocisteine is a mucoregulatory and anti-inflammatory drug found to significantly reduce COPD exacerbations. Reduction in the rate of exacerbation only became significant after 6 months of treatment with carbocisteine 300 mg three times daily in the Chinese PEACE study, which monitored COPD patients over a period of 1 year. QoL measures and exacerbation rates (mean reduction of 0.34 exacerbations per patient per year) improved at 12 months. Only 16.7% of study subjects received ICS. NNT was 6 [76].

Azithromycin taken daily at a dose of 250 mg was reported to significantly reduce the rate of COPD exacerbations in severe COPD patients over a period of 1 year. QoL measures and exacerbation rates (mean reduction of 0.35 exacerbations per patient per year) improved at 12 months. NNT was 3. Hearing loss was the most frequent adverse effect and in most, hearing did not return to baseline [77].

Shortly after this study was published, a retrospective cohort review was published in the same journal reporting a possible association between azithromycin (5 days of antibiotic therapy) and QT-prolongation with ventricular tachycardia, including episodes of torsade de pointes [78].

There were 22 sudden cardiac deaths linked to azithromycin. Daily azithromycin use to prevent COPD exacerbations may not be appropriate in every patient. Azithromycin has not yet been endorsed by any guideline or organization such as the NIH GOLD or ATS/ERS to prevent COPD exacerbations.

Narrow-spectrum for COPD & ACOS

Oxygen—Indications for long-term oxygen treatment (LTOT) in COPD have been established by the Nocturnal Oxygen Therapy Trial Group (NOTT) [79] and the Medical Research Council (MRC) [80]. Specifically, supplemental oxygen should be prescribed if arterial oxygen (PaO_2) is ≤ 55 mmHg or oxygen saturation (SpO_2) $\leq 88\%$ at rest while breathing room air. A PaO_2 of 56–59 mmHg or SpO_2 89% qualifies COPD patients for oxygen if there is evidence of pulmonary arterial hypertension, dependent edema or polycythemia (hematocrit $>56\%$) [81].

No further studies have been performed in the past 25 years to extend the results of these landmark studies. Protective effects appear to be slowing the progression to cor pulmonale and heart failure. Pulmonary oxygen toxicity remains a theoretical possibility from increased oxidative stress. The presumption is that every COPD patient who meets the inclusion criteria for NOTT will benefit from LTOT and that everyone who fails to meet those inclusion criteria will not benefit. In fact, the cutoffs for arterial oxygen concentration at 55 and 59 mmHg originate from reasonable, prospective choices made during the design of the NOTT and MRC trials and not from the analysis of data from these trials. Hence, the precision and detail of guidelines based on these inclusion criteria overstate their scientific basis.

The prednisone problem

Patients with severe asthma are most often referred to consultants for their persistent oral corticosteroids requirements, recurrent exacerbations and debilitating symptoms. It has been our experience that many patients have not received stepwise therapy as recommended by NAEPP EPR-3, have very poor technique with prescribed inhalers, untreated comorbidities or the wrong diagnosis. In our therapeutic algorithm, we use a 'clinical trial of one', using one drug at a time to perform a meaningful empiric trial and to mitigate the risk of adverse reactions from prednisone use, such as Cushing's syndrome, diabetes mellitus and osteoporosis. Approximately 40% of the SARP Clusters 4 and 5 patients who required oral corticosteroids daily (for more than 6 months) have features akin to ACOS [82]. These patients are in a 'persistent state' of exacerbation or have refractory asthma, needing albuterol several times a day to control breakthrough symptoms of cough, wheezing, chest tightness and dyspnea.

In Figure 5, we share our approach to pharmacologic treatment in those with ACOS. Persistent high-dose prednisone or methylprednisolone should prompt physicians to reassess treatment goals and seek alternatives where possible. Severe fatigue, weakness, body aches and joint pains should warn of adrenal insufficiency or Cushing's syndrome. Use of anti-inflammatory drugs that have 'corticosteroid-sparing' effects should be considered, such as LTRA or omalizumab, in severe persistent asthma. Roflumilast has not been studied as a corticosteroid-sparing agent in asthma or COPD. Severe persistent asthma with fungal sensitivities or allergic bronchopulmonary mycosis without chronic bronchiectasis may represent a specific asthma endotype that may respond to an 8-month course of itraconazole 200 mg twice daily. A large and significant improvement in QoL occurred in 60% of patients during the 32-week treatment period in the FAST study [83]. For all patients, consideration must be given to the risks associated with oral corticosteroids, including diabetes, pneumonia, osteoporosis and psychological/behavioral effects.

If a patient with asthma or ACOS is not dependent on oral cortico steroids daily and in the absence of reliable biomarkers, we rely on the patient's short-term (2–6 weeks) response to drug treatments to guide clinical decisions. For patients with ACOS not currently requiring prednisone, we recommend the following approach:

- Smoking cessation and allergen avoidance, when applicable.
- Checking total IgE and radioallergosorbent test panel to detect atopy, p- and c-ANCA for eosinophilic vasculitis, and fungal sensitivity testing. Consider a chest CT for bronchiectasis, allergic bronchopulmonary mycosis and/or abnormal DLco. With positive serology for *Aspergillus* spp. or other fungus (i.e., fungal sensitivity), consider treatment with itraconazole as described above.
- If prednisone is indicated, treat the patient with 12 days of prednisone in the late afternoon rather than the morning if not currently prescribed, for example, 40 mg $\times$ 3 days, 30 mg $\times$ 3 days, 20 mg $\times$ 3 days, 10 mg $\times$ 3 days, and return to clinic to determine response to systemic corticosteroid treatment. With a favorable response, such as symptom control, fall in FeNO by 50% or improvement in

FEV₁ by >5%, consider leaving the patient on low-dose prednisone of 1–3 mg daily in addition to high-dose ICS + LABA combination.

- Add the LAMA inhaler tiotropium and measure FEV₁ in a scheduled follow-up visit 2 weeks later. Tiotropium and a LABA have an additive effect on airway bronchodilatation. Discontinue LABA if there is no clinical benefit, continue tiotropium and rely on albuterol if there is concern for LABA toxicity.
- Treat with omalizumab if serum IgE is elevated between 30 and 700 IU/l and radioallergosorbent test panel is positive for a perennial aeroallergen. It is important to begin treatment within 6 weeks of consultation because of the 6 months needed to determine efficacy. During this period, continue evaluating responses to other drugs to spare the patient from high-dose ICS and/or prednisone. Monitor in clinic for anaphylaxis for 2 h after the first three injections (captures 76% of anaphylactic reactions). Discontinue omalizumab if there is no clinical benefit.
- Continue montelukast only if the patient derives clear clinical benefit. In place of montelukast, consider zileuton SR 600 mg twice daily for 2–6 weeks in patients with asthma but not in those with COPD. Discontinue it if there is no clinical benefit or reduction in FeNO (goal reduction by 50%).
- Consider low-dose theophylline to reduce corticosteroid resistance, keeping serum theophylline levels <5–10 mg/l. Discontinue it after 2–6 weeks if there is no clinical benefit.
- Consider roflumilast to reduce COPD-related exacerbations. It is not currently FDA approved for asthma despite evidence of a modest bronchodilator effect and reduction in sputum eosinophils and neutrophils.
- Consider sputum induction, or fiberoptic bronchoscopy with bronchoalveolar lavage, endobronchial and/or transbronchial biopsies to confirm eosinophilic or noneosinophilic airway inflammation [84].
- Consider Churg–Strauss syndrome and other pulmonary eosinophilic syndromes in patients with persistent corticosteroid dependence who recur after corticosteroid discontinuation or who have minimal or no response to therapy.
- Consider bronchial thermoplasty in patients who fail to improve, or those who decline omalizumab. A requirement for bronchial thermoplasty includes a postbronchodilator FEV₁ of >60% predicted.

For patients requiring prednisone daily, recommendations 3, 4, 5, 6 and 11 above should be considered in addition to evaluation for adrenal insufficiency or Cushing's syndrome. For the prednisone-dependent adult with severe asthma with a FEV₁ <60% predicted and who fails to qualify for omalizumab, consider azithromycin in addition to the lowest effective dose of prednisone. Immunotherapy against detected aeroallergens is considered adjunctive care by the NAEPP EPR-3 but may have utility in very difficult-to-control cases.

For those on continued prednisone therapy or who need a corticosteroid-sparing regimen and are refractory to omalizumab, other monoclonal antibodies may be considered. Patients with severe asthma and evidence of eosinophilic airway inflammation may benefit from anti-IL-5 antibody therapy with mepolizumab [85,86]. Chemokine and cytokine antagonists are appealing as immunomodulators (Box 2). Use of cyclophosphamide 1–5 mg/kg daily or methotrexate 15 mg per week should be considered with extreme caution because of adverse drug effects and only after thorough consultation. Nutritional supplementation with fish oils and vitamin D are also under active clinical investigation.

Acknowledgements

The authors gratefully acknowledge Chue Xiong at the University of California, Davis School of Medicine (CA, USA), for her expert help in the preparation of the manuscript.

Financial & competing interests disclosure

S Louie has received financial support from AstraZeneca, Boehringer Ingelheim, Forest, Genentech, GSK and Merck. He has received speaker's honoraria for asthma and COPD from Pfizer. TE Albertson has received support from Boehringer Ingelheim and GSK, and speaker's honoraria for COPD from Pfizer. AA Zeki has received research support from the NIH, the Tobacco-Related Disease Research Program and the American Asthma Foundation. M Schivo has received research support from the NIH. M Avdalovic has received research support from Merck, Novartis and the NIH. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

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Box 1.**Risk factors and symptoms related to asthma–chronic obstructive pulmonary disease overlap syndrome with suggested major and minor criteria for clinical recognition.**

- Risk factors
 - Atopy; for example, hay fever, elevated total IgE, positive RAST testing or intradermal allergen testing
 - History of current or past cigarette smoking (>10 pack-years)
 - Severe persistent asthma during childhood
- Symptoms
 - Chronic cough or wheezing with or without sputum (early symptom)
 - Dyspnea or exercise intolerance (late symptom)
 - Reduction in daily activities of living
 - Frequent need for inhaled albuterol
 - Frequent acute exacerbations despite adherence to standard pharmacotherapy
- Major criteria
 - A physician diagnosis of asthma and chronic obstructive pulmonary disease in the same patient
 - History or evidence of atopy; for example, hay fever, elevated total IgE
 - Age ≥ 40 years
 - Smoking >10 pack-years
 - Postbronchodilator FEV_1 <80% predicted and FEV_1/FVC < 70%
- Minor criteria
 - 15% increase in FEV_1 or ≥ 12% and ≥ 200 ml increase in FEV_1 postbronchodilator treatment with albuterol

FEV_1 : Forced expiratory volume in 1 s; FVC: Forced vital capacity; RAST: Radioallergosorbent test.

Box 2.**Current and emerging drug treatments for asthma and chronic obstructive pulmonary disease and dual utility in asthma–chronic obstructive pulmonary disease overlap syndrome.**

- Smoking aids
 - Nicotine replacement treatments^{†‡§}
 - Bupropion (Zyban® [GlaxoSmithKline, London, UK])^{†‡§}
 - Varenicline (Chantix® [Pfizer, NY, USA])^{†‡§}
 - Nicotine vaccines
- Bronchodilators
 - Short-acting
 - ◆ SABA, for example, racemic albuterol[§], levalbuterol (Xopenex® [Sunovion Pharmaceuticals, MA, USA])[§]
 - ◆ SAMA, for example, ipratropium (Atrovent® [Boehringer Ingelheim, Ingelheim, Germany])[‡]
 - ◆ Combination SABA + SAMA, that is, combination albuterol + ipratropium (Combivent® [Boehringer Ingelheim, Ingelheim, Germany])[‡]
 - Long-acting
 - ◆ LABA[#], for example, salmeterol (Serevent® [GlaxoSmithKline, London, UK])^{‡§}, formoterol (Foradil® [Novartis, Basel, Switzerland])^{‡§}, arformoterol inhalation solution (Brovana® [Dainippon Sumitomo, Osaka, Japan]), formoterol inhalation solution (Perforomist® [Dey Pharma, NJ, USA]), indacaterol (Arcapta® [Novartis, Basel, Switzerland])[‡], vilanterol, carmoterol, milveterol, BI-1744-CL, PF-00610355, LAS-100977
 - ◆ LAMA, for example, tiotropium (Spiriva® [Boehringer Ingelheim, Ingelheim, Germany])^{‡§}, aclidinium (Tudoraza® [Forest Pharmaceuticals, NY, USA] or Eklira® [Almirall, Barcelona, Spain])[‡], glycopyrronium, darotroprum, dexpirronium, umeclidinium, QAT-370, TD-4208
- Emerging treatments
 - MABA – dual pharmacophore with long-acting muscarinic antagonist and β_2 agonist pharmacology^{†‡§}
 - GSK-961081 (GlaxoSmithKline, London, UK), formerly TD-5959

- THRX-200495 (Theravance, CA, USA)
- IL-4 inhibitor pitrakinra[†]
- IL-5 inhibitors mepolizumab[†], reslizumab[†]
- IL-13 inhibitor lebrikizumab[†]
- Statins
 - ◆ Simvastatin
- Other drugs
 - ◆ Immunosuppressive agents, for example, cyclosporin A and antimetabolite methotrexate
 - ◆ TNF- α inhibitor
 - ◆ NF- κ B inhibitors – p38 MAPK inhibitors^{†‡§}
 - ◆ Proteinase inhibitors targeting matrix metalloproteinase and neutrophil elastase
 - ◆ Antioxidants
- Inhaled corticosteroids (in order of increasing potency; equal efficacy when dose-adjusted)^{†§}
 - Triamcinolone (Azmecort® [Abbott Laboratories, IL, USA])
 - Beclometasone (Qvar® [IVAX, FL, USA])
 - Budesonide (Pulmicort® [AstraZeneca, London, UK])
 - Ciclesonide (Zetonna® [Sunovion Pharmaceuticals, MA, USA])
 - Mometasone (Asmanex® [Merck, NJ, USA])
 - Fluticasone propionate (Flovent® [GlaxoSmithKline, London, UK])
- Double therapy (ICS + LABA) in single delivery device[#]
 - Fluticasone propionate + salmeterol (Seretide® [GlaxoSmithKline, London, UK] or Advair® [GlaxoSmithKline, London, UK])^{‡§¶#}
 - Fluticasone furoate + vilanterol (Relovair® [GlaxoSmithKline, London, UK])[#]
 - Budesonide + formoterol (Symbicort® [AstraZeneca, London, UK])^{‡§¶#}
 - Mometasone + formoterol (Dulera® [Merck, NJ, USA])^{§†#}
 - Mometasone + indacaterol[#]
- Double therapy (LABA + LAMA) in single delivery device[#]
 - Carmoterol + tiotropium

- Formoterol + aclidinium
- Formoterol + glycopyrronium
- Indacaterol + glycopyrronium
- Vilanterol + umeclidinium
- Milveterol + darotropium
- Vilanterol + darotropium
- Triple therapy (ICS + LABA + LAMA or PDE-4 inhibitor + LABA + LAMA) in single delivery device
 - Mometasone + indacaterol[#] + glycopyrronium
 - Fluticasone furoate + milveterol or vilanterol[#] + darotropium or umeclidinium
 - Ciclesonide + formoterol[#] + tiotropium
- Leukotrine modifiers
 - Leukotriene receptor antagonists^{†§}
 - ◆ Montelukast (Singulair® [Merck, NJ, USA])
 - ◆ Zafirlukast (Accolate® [AstraZeneca, London, UK])
 - ◆ Pranlukast (Azlaire® [Schering-Plough] or Onon® [Ono Pharmaceutical Co., Ltd.])
 - 5-lipoxygenase inhibitor^{†§}
 - ◆ Zileuton (Zyflo®)
- Phosphodiesterase-4 inhibitors
 - Roflumilast (Daliresp® [Forest Pharmaceuticals, NY, USA] or Daxas® [Takeda, Zurich, Switzerland])^{†§}
- Methylxanthine
 - Theophylline^{†‡§}
- Monoclonal antibodies and immunomodulators
 - Omalizumab (Xolair® [Novartis, Basel, Switzerland])[†]
- Vaccines
 - NTHi oral immunotherapeutic (HI-164OV) against *Hemophilus influenzae*[‡]
 - Pneumococcal vaccine
 - Influenza vaccine
- Antibiotics

- Azithromycin^{†‡§}
- Azole antifungal agents, itraconazole[†]
- Mucoregulators
 - Carbocisteine[‡]

[†]Asthma only.

[‡]Chronic obstructive pulmonary disease only.

[§]Both or asthma–chronic obstructive pulmonary disease overlap syndrome.

[¶]Only fluticasone 250 µg/salmeterol 40 µg fixed combination dry powder inhaler and budesonide 160 µg/formoterol 4.5 µg fixed combination metered-dose inhaler are US FDA approved for chronic obstructive pulmonary disease in the USA.

[#]FDA black box warning alert contraindicate their use as monotherapy in asthma patients and warning their use alone or in combination with other medications that cause asthma deaths.

ICS: Inhaled corticosteroids; LABA: Long-acting β_2 agonist; LAMA: Long-acting muscarinic receptor antagonist; SABA: Short-acting β_2 agonist; SAMA: Short-acting muscarinic receptor antagonist.

Key issues

- Patients with asthma–COPD overlap syndrome (ACOS) have the combined risk factors of smoking and atopy, are generally younger than patients with COPD, have more frequent acute exacerbations than lone COPD and require more healthcare services, despite a lower burden of cigarette smoking.
- ACOS may be recognized with a physician diagnosis of asthma and COPD in the same patient; history or evidence of atopy, for example, hay fever, elevated total IgE, age <40 years; smoking >10 pack-years, postbronchodilator FEV₁ <80% predicted; and FEV₁/FVC <70%. A >15% increase in FEV₁ or >12%, and >200 ml increase in FEV₁ postbronchodilator.
- Pharmacotherapeutic considerations require an integrated approach, first to identify the relevant clinical phenotype(s), then to determine the best available therapies by integrating reasoned clinical experience and logical extrapolation from the existing literature in asthma and COPD.
- Current published literature and guidelines attempt to provide direction but international consensus is needed on diagnostic criteria, design of clinical drug trials and treatment algorithms for ACOS.
- Future treatments will be based on pathobiologic mechanisms in ACOS patients, and on mitigating risk factors common to all three syndromes: asthma, COPD and ACOS.
- Emerging therapies should be endotype-specific, and future guidelines for this syndrome will be informed by clinical trials that link clinical phenotypes with pathobiologic patterns.

Figure 1.

Prevalence of obstructive airway disease in the University of California Davis Medical Center general pulmonary clinics.

* $p = 0.0009$; ** $p < 0.0001$; *** $p < 0.0001$ by Fisher's exact test. 'Other' represents a combination of bronchitis, bronchiectasis, bronchiolitis and/or cystic fibrosis cases.

ACOS: Asthma–chronic obstructive pulmonary disease overlap syndrome; COPD: Chronic obstructive pulmonary disease; NS: Not significant.

Adapted with permission from [2].

Figure 2.

Prevalence of obstructive airway disease in the University of California Davis Medical Center severe asthma clinics.

* $p = 0.0009$; ** $p < 0.0001$; *** $p < 0.0001$ by Fisher's exact test. 'Other' represents a combination of bronchitis, bronchiectasis, bronchiolitis and/or cystic fibrosis cases.

ACOS: Asthma–chronic obstructive pulmonary disease overlap syndrome; COPD: Chronic obstructive pulmonary disease.

Adapted with permission from [2].

Figure 3.

Percentage of frequent and severe exacerbations in subjects with chronic obstructive pulmonary disease compared with subjects with chronic obstructive pulmonary disease with asthma.

* $p < 0.0001$ for the difference between COPD and COPD with asthma.

COPD: Chronic obstructive pulmonary disease.

Adapted with permission from [4].

Figure 4.
Pharmacotherapeutic targets in asthma–chronic obstructive pulmonary disease overlap syndrome.
COPD: Chronic obstructive pulmonary disease.

Figure 5. Algorithm of potential pharmacotherapeutic considerations in asthma–chronic obstructive pulmonary disease overlap syndrome.
 5-LO: 5-lipoxygenase; Ab: Antibody; FEV₁: Forced expiratory volume in 1 s; FeNO: Fractional exhaled nitric oxide; LABA: Long-acting β_2 agonist; LAMA: Long-acting muscarinic receptor antagonist; MABA: Muscarinic antagonist- β_2 agonist; SABA: Short-acting β_2 agonist; SAMA: Short-acting muscarinic receptor antagonist.
 Adapted with permission from [2].

Figure 6.

Overview and considerations in the approach to asthma–chronic obstructive pulmonary disease overlap syndrome.

Red arrows indicate that patients with asthma–COPD overlap syndrome can be found in asthma populations and COPD populations.

5-LO: 5-lipoxygenase; AHR: Abnormal hyper-responsiveness; COPD: Chronic obstructive pulmonary disease; ICS: Inhaled corticosteroids; LABA: Long-acting β_2 agonist; LAMA: Long-acting muscarinic receptor antagonist; LTRA: Leukotriene receptor antagonist; LVRS: Lung volume reduction surgery.

Adapted with permission from [2].

Table 1.

Comparing asthma, chronic obstructive pulmonary disease and asthma–chronic obstructive pulmonary disease overlap syndromes.

Syndrome	Asthma (severe) [105]	ACOS	COPD [106]
Demographics	>40 years Women > men Nonsmoker or <5 pack years Obesity Atopy typical Rhinosinusitis GERD Frequent albuterol use Exercise limited in between attacks Dependence on prednisone Hallmark problem: frequent exacerbations	>40 years; 50–65 years Past or current smoker >10 pack-years Atopy present Rhinosinusitis GERD Exercise very limited Hallmark problem: very frequent exacerbations > COPD alone	65 years if not younger Past or current smoker >10 pack-years No atopy GERD Multiple daily albuterol Exercise very limited Oxygen dependence Hallmark problem: exacerbations and exercise intolerance
Pathophysiology	Intermittent to chronic moderate-to-severe airflow obstruction FEV ₁ /FVC <0.70 FEV ₁ <68% predicted, or <65% after albuterol SARP cluster 3, 4 or 5 DLco normal FeNO >50 ppb 3% sputum eosinophils Exacerbations >3/year	Intermittent to chronic moderate-to-severe airflow obstruction FEV ₁ /FVC <0.70 FEV ₁ <68% predicted, or <65% after albuterol DLco normal or low FeNO >25–50 ppb Static hyperinflation Exacerbations >3–5/year Frequent nocturnal awakenings 4/week	Chronic airflow obstruction moderate to severe (GOLD II-IV) FEV ₁ /FVC <0.70 DLco <80% predicted FeNO <25 ppb Static and dynamic hyperinflation Exacerbations >2/year after FEV ₁ <50% Infrequent nocturnal awakenings Pulmonary HTN late
Pathobiology	Airway inflammation: eosinophils > neutrophils Mast cells CD4 ⁺ T lymphocytes Smooth muscle hyperplasia/hypertrophy No emphysema Basement membrane thickening IgE, IL-4, IL-5, IL-13, eosinophil	Airway inflammation: eosinophils + neutrophils, CD4 ⁺ T lymphocytes, CD8 ⁺ T lymphocytes Alveolar macrophages, smooth muscle hyperplasia/hypertrophy ± emphysema Peribronchiolar fibrosis IgE, IL-4, IL-5, IL-18, IL-1B, IL-8, IL-6, TNF-α, cotaxin, proteases	Emphysema with alveolar destruction Airway inflammation: neutrophils > eosinophils CD4 ⁺ T lymphocytes, CD8 ⁺ T lymphocytes Alveolar macrophages Mast cells? Peribronchiolar fibrosis IL-1β, IL-8, IL-6, TNF-α, proteases
First-line pharmacotherapy and treatments	ICS ICS + LABA [†]	ICS ± LABA Smoking cessation Pulmonary rehabilitation	Bronchodilators LABA or LABA or both Smoking cessation Pulmonary rehabilitation
Current add-on pharmacotherapy	LABA [†] , LAMA, LTRA, theophylline, omalizumab [†] , prednisone	LABA, LAMA, LTRA, or roflumilast or theophylline, omalizumab [†] , prednisone	ICS or roflumilast theophylline
Emerging treatments	Anti-IL-5, anti-IL-13 ICS + LABA [†] once daily Azithromycin Vaccines Bronchial thermoplasty	Refer to asthma and COPD emerging treatments Consider using FeNO to endotype Bronchial thermoplasty	LAMA + LABA once daily Carbocisteine Azithromycin Anti-IL-8, p39 protein kinase inhibitors <i>Haemophilus influenzae</i> vaccine Endobronchial valves Lung transplantation

[†]US FDA black box warning alert.

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ACOS: Asthma-COPD overlap syndrome; COPD: Chronic obstructive pulmonary disease; DLco: Carbon monoxide diffusing capacity; FeNO: Fractional exhaled nitric oxide; FEV₁: Forced expiratory volume in 1 s; FVC: Forced vital capacity; GERD: Gastroesophageal reflux disease; HTN: Hypertension; ICS: Inhaled corticosteroids; LABA: Long-acting β_2 agonist; LAMA: Long-acting muscarinic receptor antagonist; LTRA: Leukotriene receptor antagonist; SARP: Severe Asthma Research Program.

Table 2.

Number needed to treat to prevent acute moderate-to-severe exacerbations of asthma or chronic obstructive pulmonary disease.

Drug or treatment	NNT	Comment	Ref.
COPD study Tiotropium or placebo added to ongoing LABA ± ICS ± theophylline	8 to prevent one exacerbation per year + 14% reduction in exacerbation 7 to prevent one exacerbation per year in GOLD II COPD + 20% reduction in exacerbations	4-year study 62% on ICS 60% on LABA n = 5992 No change annual decline in FEV ₁ across GOLD II, III and IV	[25]
COPD study Fluticasone 500 µg + salmeterol compared with salmeterol	2 to prevent one exacerbation per year 35% reduction in exacerbations	44-week study n = 998 Fluticasone/salmeterol 500 µg/50 µg No tiotropium used Theophylline permitted	[57]
COPD study Fluticasone 500 µg + salmeterol vs fluticasone alone vs salmeterol alone vs control	3 to prevent one exacerbation per year vs placebo 8 to prevent one exacerbation per year vs salmeterol 25% reduction in exacerbations	3-year study n = 6112 No anticholinergics	[24]
COPD study Fluticasone 250 µg + salmeterol vs salmeterol alone	2 to prevent one exacerbation per year vs salmeterol alone 30.5% reduction in exacerbations	1-year study n = 782 No anticholinergics or other maintenance drugs	[58]
COPD study Tiotropium or salmeterol added to usual care, including inhaled corticosteroids	24 to prevent one exacerbation per year vs salmeterol	1-year study	[50]
COPD study Tiotropium added to usual care COPD treatments	13 to prevent one exacerbation per year 38 to prevent one hospitalization per year	Nine trials n = 8002 Tiotropium reduced COPD exacerbations, hospitalizations, improved quality of life and symptoms and may have slowed the decline in FEV ₁	[53]
COPD study Roflumilast vs placebo added to SABA (99–100%) ± SAMA (35–37%) ± LABA (44–45%)	4 to prevent one exacerbation per year 18% reduction in exacerbations 5 to prevent one exacerbation per year 15% reduction	1-year study n = 1571 No ICS during either trial 1-year study n = 1525	[70]
COPD study Theophylline vs LABA Theophylline vs ICS	9 to prevent one exacerbation per year with theophylline vs LABA 5 to prevent one exacerbation per year with ICS vs theophylline	n = 36,492 reconstructed from healthcare database in COPD patients aged 50 years	[74]
COPD study Azithromycin or placebo added to usual care COPD treatments	3 to prevent one exacerbation per year	Exacerbations reduced despite development of antibiotic resistance n = 1142	[77]
COPD study Carbocisteine added to usual care COPD treatments, including inhaled corticosteroids	6 to prevent 1 exacerbation per year	1-year study Mucolytic 1500 mg per day n = 709	[76]
Asthma study Fluticasone + salmeterol compared with fluticasone	15 to prevent one exacerbation per year	1-year study Fluticasone titrated for asthma control every 12 weeks	[23]

Drug or treatment	NNT	Comment	Ref.
Asthma study Omalizumab added to ICS + LABA + other controllers	3 to prevent one exacerbation per year 2 to prevent one severe exacerbation per year 2 to prevent one emergency visit	n = 3421 28-week study n = 419 Add-on omalizumab significantly reduced clinically significant exacerbation rates by 26%, severe exacerbation rates by 50% and emergency visit rates by 44%	[68]
Asthma study Omalizumab added to ICS + LABA	10 to prevent one exacerbation per year 33 to prevent one hospitalization per year 5 for one successful corticosteroid discontinuation	Eight trials n = 3429 US\$12,000 per year Serious adverse effects omalizumab (3.8%) vs placebo (5.3%). No increased risk of malignancy, hypersensitivity or cardiovascular effects	[66]
Asthma study Salmeterol or montelukast added to ICS	38 to prevent one exacerbation per year for salmeterol vs LTRA	Seventeen trials n = 5895 Add-on LABA superior to LTRA in preventing exacerbations, symptom control and need for rescue albuterol	[87]
Asthma study Budesonide or placebo + usual therapy in mild persistent asthma	45 to prevent one exacerbation in 3 years	5-year study n = 7241 age 5–66 years	[88]
Asthma study Bronchial thermoplasty in severe persistent asthma despite step 5 of the NIH NAEPP EPR-3 treatment guidelines	6 to prevent one exacerbation per year 7 to improve quality of life	n = 288	[89]
COPD study Patient self-management vs usual care	2 to prevent one hospitalization per year 39.8% reduction in hospital admissions for COPD	1-year study Emergency department visits were reduced by 41.0% and unscheduled physician visits by 58.9%	[33]

NNT rounded to whole number. For comparison, NNT for primary prevention of nonfatal myocardial infarction or cardiovascular death is 69 for lipid-lowering drugs and NNT for cardiovascular events for statins is 17 and 30 for death [90].

COPD: Chronic obstructive pulmonary disease; FEV₁: Forced expiratory volume in 1 s; ICS: Inhaled corticosteroids; LABA: Long-acting β_2 agonists; LTRA: Leukotriene receptor antagonist; NNT: Number needed to treat; SABA: Short-acting β_2 agonist; SAMA: Short-acting muscarinic receptor antagonist.