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MiniReview

Diagnosis and Pharmacotherapy of Stable Chronic Obstructive Pulmonary Disease: The Finnish Guidelines

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Abstract: The Finnish Medical Society Duodecim initiated and managed the update of the Finnish national guideline for chronic obstructive pulmonary disease (COPD). The Finnish COPD guideline was revised to acknowledge the progress in diagnosis and management of COPD. This Finnish COPD guideline in English language is a part of the original guideline and focuses on the diagnosis, assessment and pharmacotherapy of stable COPD. It is intended to be used mainly in primary health care but not forgetting respiratory specialists and other healthcare workers. The new recommendations and statements are based on the best evidence available from the medical literature, other published national guidelines and the GOLD (Global Initiative for Chronic Obstructive Lung Disease) report. This guideline introduces the diagnostic approach, differential diagnostics towards asthma, assessment and treatment strategy to control symptoms and to prevent exacerbations. The pharmacotherapy is based on the symptoms and a clinical phenotype of the individual patient. The guideline defines three clinically relevant phenotypes including the low and high exacerbation risk phenotypes and the neglected asthma–COPD overlap syndrome (ACOS). These clinical phenotypes can help clinicians to identify patients that respond to specific pharmacological interventions. For the low exacerbation risk phenotype, pharmacotherapy with short-acting β_2-agonists (salbutamol, terbutaline) or anticholinergics (ipratropium) or their combination (fenoterol–ipratropium) is recommended in patients with less symptoms. If short-acting bronchodilators are not enough to control symptoms, a long-acting β_2-agonist (formoterol, indacaterol, olodaterol or salmeterol) or a long-acting anticholinergic (muscarinic receptor antagonists; aclidinium, glycopyrronium, tiotropium, umeclidinium) or their combination is recommended. For the high exacerbation risk phenotype, pharmacotherapy with a long-acting anticholinergic or a fixed combination of an inhaled glucocorticoid and a long-acting β_2-agonist (budesonide–formoterol, beclomethasone dipropionate–formoterol, fluticasone propionate–salmeterol or fluticasone furoate–vilanterol) is recommended as a first choice. Other treatment options for this phenotype include combination of long-acting bronchodilators given from separate inhalers or as a fixed combination (glycopyrronium–indacaterol or umeclidinium–vilanterol) or a triple combination of an inhaled glucocorticoid, a long-acting β_2-agonist and a long-acting anticholinergic. If the patient has severe-to-very severe COPD (FEV_1 < 50% predicted), chronic bronchitis and frequent exacerbations despite long-acting bronchodilators, the pharmacotherapy may include also roflumilast. ACOS is a phenotype of COPD in which there are features that comply with both asthma and COPD. Patients belonging to this phenotype have usually been excluded from studies evaluating the effects of drugs both in asthma and in COPD. Thus, evidence-based recommendation of treatment cannot be given. The treatment should cover both diseases. Generally, the therapy should include at least inhaled glucocorticoids (beclomethasone dipropionate, budesonide, ciclesonide, fluticasone furoate, fluticasone propionate or mometasone) combined with a long-acting bronchodilator (β_2-agonist or anticholinergic or both).

The Finnish Medical Society Duodecim has created a system for the production of national guidelines on the most important diseases. These guidelines provide the basis of evidence-based treatment of about 100 common health problems and are based on a rigorous evaluation of evidence and production of the guidelines in a specific format including formal level of evidence statements (A–D; see table 1) [1], and this level of evidence is also referred in the current MiniReview. The major difference between the current guideline and most other guidelines for chronic obstructive pulmonary disease (COPD) is that the short reviews of the literature presenting the evidence supporting the claim for a certain level of evidence (A–D) are publicly available [1,2]. These guidelines and statements (in the Finnish language) are published on the website of the medical society Duodecim [1,2] and are available to all physicians as well as to the general public in Finland. In addition, patient versions are occasionally published. During summer 2012, the Finnish Medical Society Duodecim and the Finnish

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Table 1.

Grading of the evidence in the Current Care Guidelines.

Level of evidence	Description (*verbal expression in the text*)
A	Strong research-based evidence (multiple, relevant, high-quality studies with homogeneous results – e.g. two or more randomized, controlled trials or a systematic review with clearly positive results)
B	Moderate evidence (e.g. one randomized, controlled trial or multiple adequate studies) (. . .*apparently*. . .)
C	Limited research-based evidence (e.g. controlled, prospective studies) (. . .*may*. . .)
D	No evidence (e.g. retrospective studies or the consensus reached in the absence of good-quality evidence)

Adapted from reference [1].

Respiratory Society invited members to a group aiming to update the previous guideline on COPD. The production of the novel guideline was started in October 2012, and the final version of the guideline (in Finnish) was accepted and published on 13 June 2014 after a long review process [2].

In Finland, the diagnostics and treatment of common respiratory diseases such as asthma and COPD are mainly performed in primary health care by general practitioners, and only a part of the patients are treated by respiratory specialists. The Finnish Medical Society Duodecim represents the whole medical community in Finland, and the society necessitates that the guideline should serve especially the general practitioners working in primary health care. However, the guideline is also widely used by respiratory specialists and other healthcare specialists such as nurses and pharmacists. Thus, the main requirements for the guideline were that it should be evidence based, accurate, clear and simple enough to be used in a busy general practice.

The need to update the guideline for the treatment of COPD was aroused by the prevalence of COPD in the Finnish patients and its importance and costs to patients and to the healthcare system as well as the paradigm shift in the treatment of COPD started by the GOLD (Global Initiative for Chronic Obstructive Lung Disease) report [3]. This guideline greatly owes to the international GOLD report [3] as well as to the innovative guideline for COPD by the Spanish Respiratory Society [4]. The present guideline introduces a modified and hopefully, simplified version of pharmacological treatment based on the assessment of exacerbation risk presented in the GOLD report [3] and Spanish guideline [4]. It takes into the account the neglected phenotype of COPD–asthma as presented in the Spanish COPD guideline [4,5] or asthma–COPD overlap syndrome (ACOS) as termed by the recent GINA report [6]. Asthma and COPD are generally diagnosed, treated and managed by the same personnel (nurses and general practitioners) in Finland. As there are some crucial differences in the treatment of these two common diseases, accurate diagnosis and clear treatment guidelines are of utmost importance. Thus, in the preparation of the present guideline, the diagnostic section was co-ordinated with the recently published asthma guideline as three members served in this group (H.K., T.H. and L.L.) who were also involved in the production of the asthma guideline [7]. Special attention was drawn to the diagnosis of COPD, differential diagnosis between asthma and COPD, and the inclusion of the ACOS. In addition, the pharmacological treatment section was developed to pursue readiness, simplicity and in-depth precision at the same time. This Finnish COPD guideline in the English language covers only a part of the original guideline [2,8,9], that is the diagnostics, comprehensive assessment and pharmacological treatment of stable COPD. Other sections such as epidemiology, screening, tobacco cessation, oxygen therapy, ventilatory support, surgical treatments, pulmonary rehabilitation, management of acute exacerbations and palliative care can be found in the original document in Finnish [2,9]. This version of the guideline has been updated to contain some novel compounds (e.g. umeclidinium), fixed combinations of long-acting bronchodilators (glycopyrronium–indacaterol and umeclidinium–vilanterol) and fixed combinations of inhaled glucocorticoids (ICS) and long-acting β_2-agonists (beclomethasone dipropionate–formoterol and fluticasone furoate–vilanterol) not included in the earlier published Finnish version [2,8] and now available in Finland. In addition, new relevant literature has been cited.

Diagnostics

The diagnosis of COPD is based on relevant exposure history, symptoms and airway obstruction that is not fully reversible (post-bronchodilator forced expiratory volume in one-second/forced vital capacity < 0.70; $FEV_1/FVC < 0.70$).

Evaluation of predisposing factors.

The following predisposing factors should be assessed in the diagnostic evaluation: smoking history (in pack-years), current smoking, passive smoking, occupational exposures, previous respiratory infections, asthma and respiratory diseases in the family.

Symptoms.

Typical symptoms of COPD include dyspnoea, chest tightness, wheezing, cough and sputum production [3], but the diagnosis of COPD cannot be based on symptoms alone, as some patients are symptom free and similar symptoms can be caused by other diseases [10]. However, symptoms suggestive of COPD in an individual with exposure to tobacco or other risk factors should lead to spirometry and other diagnostic evaluations. In patients with established COPD, the level of symptoms and the presence of exacerbations should be assessed as these are used to guide the treatment

[3]. COPD is a progressive disease and symptoms tend to worsen, especially if the patient continues smoking, and dyspnoea at rest or light exercise, cough, weight loss and frequent exacerbations are often present in advanced severe-to-very severe COPD [11].

Physical examination.
The diagnosis of COPD cannot be based on clinical signs, but these can be suggestive of COPD and its degree of severity [3]. Wheezing may be heard during auscultation of the chest, but pulmonary sounds can also be normal. Increased respiratory rate at rest, the use of accessory respiratory muscles and signs of right-sided heart failure may be present in severe COPD.

Pulmonary function testing.
In diagnosing COPD, spirometry should be conducted with bronchodilation test. COPD can be diagnosed if FEV_1/FVC is <0.70 in a post-bronchodilation spirometry [3]. This criterion causes some over-diagnosis in elderly people [12,13] and possibly also in women [14] and under diagnosis in individuals younger than 45 years [13], but it is sensitive in detecting COPD clinically assessed by a physician [15–17]. This criterion is also associated with mortality risk [18].

Significant reversibility in the bronchodilation test (FEV_1 increases at least 12% and 200 ml) can be detected in approximately 25–50% of individuals with COPD (see Differential diagnosis below). Classification of severity of airway obstruction is presented in table 2, but this is only one aspect of the clinical severity of COPD.

Radiological imaging.
The diagnosis of COPD cannot be based on chest X-ray, but a chest X-ray should be included in the initial evaluation to exclude other diseases such as pulmonary cancer, tuberculosis, pneumonia, heart failure and pleural diseases.

In mild COPD, chest X-ray is almost always normal. In advanced disease flattening of the diaphragm, long narrow heart, over-inflation with thinning of blood vessels and emphysematous bullae can be seen. Computerized tomography of the chest is not routinely needed, but may be used by specialists in cases of problematic differential diagnosis to detect bronchiectasis and in the evaluation for surgical treatment of COPD [19].

Blood tests and sputum cultures.
There are no specific blood tests to be used in diagnosing COPD, but some basic tests may be used to rule out other diseases and to assess infections and respiratory failure during acute exacerbations. Bacterial culture of sputum is not useful in stable COPD. If COPD is found in a person with exceptionally young age (<45 years) or with a low smoking history (<20 pack-years), serum levels of alpha-1-antitrypsin (A1AT) should be measured to rule out alpha-1-antitrypsin deficiency. This recommendation may differ from that of other guidelines [3]. However, screening for A1AT is not recommended for all patients in Finland, because there is no A1AT replacement therapy available in Finland. Thus the only relevant therapeutic option is counselling for smoking cessation and the smoking cessation is recommended for all patients with COPD despite the knowledge of A1AT levels.

Comprehensive evaluation of the patient.
Symptoms, quality of life and the impact of the disease can be assessed with validated questionnaires such as COPD Assessment Test® (CAT®) and modified Medical Research Council Dyspnea Scale (mMRC) [3]. Six-minute walking test or ergometry can be used to assess exercise tolerance. The clinical severity of COPD is assessed based on the degree of airway obstruction, level of symptoms, exacerbations and co-morbidities (table 2). Extra-pulmonary manifestations and co-morbidities such as cardiovascular diseases, metabolic syndrome, osteoporosis and depression are more prevalent in individuals with COPD than in non-COPD individuals with

Table 2.
Classification of the severity of obstruction and the clinical severity of chronic obstructive pulmonary disease (COPD).

	Severity of obstruction (assessed after bronchodilation)	Clinical severity of COPD
Mild	$FEV_1 \geq 80\%$ predicted	Good quality of life (CAT® < 10), no frequent exacerbations and FEV_1 >50% predicted
Moderate	$50\% \leq FEV_1 < 80\%$	One of the following:
Severe	$30\% \leq FEV_1 < 50\%$	• $FEV_1 < 50\%$ predicted • At least two exacerbations a year or one hospitalization because of COPD • COPD has a medium impact on life (e.g. CAT® ≥ 10 points) or causes poor quality of life or impaired exercise tolerance
Very severe	$FEV_1 < 30\%$	One of the following: • $FEV_1 < 30\%$ predicted • Chronic respiratory failure • Frequent exacerbations or hospitalizations regardless of treatment to COPD • COPD has a high or very high impact on life (e.g. CAT® ≥ 20 points) or causes very poor quality of life or exercise tolerance

similar smoking history. Nutritional status and especially unintended loss of weight should be assessed.

Differential diagnosis.
The most important differential diagnoses include asthma, chronic bronchitis, lower airway infections (including tuberculosis), lung cancer, interstitial lung diseases and heart diseases.

A common diagnostic problem is to distinguish between asthma and COPD. Although these diseases are often treated with the same medication, they differ in basic pathology, aetiology and prognosis. COPD and asthma are often found in the same individual, and in smoking asthma patients, the cellular components of inflammation may resemble that found in COPD [3,6]. The differential diagnosis of asthma and COPD cannot be based on pulmonary function tests alone, but a comprehensive approach including smoking history, symptoms, co-morbidities and family history is needed [3,6].

Bronchodilation test in spirometry cannot reliably distinguish between asthma and COPD [3], as asthmatic individuals do not always present with significant reversibility and approximately 25–50% of individuals with COPD have significant reversibility [20–22].

Glucocorticoid therapy test does not always differentiate between asthma and COPD [23], as a considerable proportion of individuals with COPD benefit from ICS [24]. On the other hand, some of the asthmatic individuals are not responsive to ICS alone [25]. However, if an individual patient clearly benefits from using ICS (i.e. as assessed based on improvement in lung function or based on a reduction of symptoms or exacerbations), it should be continued regardless of the diagnosis (asthma or COPD). As the response to oral glucocorticoids does not predict responsiveness to ICS [26,27], the possible treatment trials should be conducted using ICS at moderate (to high) doses for (4 to) 8 weeks.

Normalization of lung function by ICS treatment excludes COPD and strongly supports the diagnosis of asthma. If the lung function is not significantly changed by ICS treatment, the diagnosis is more likely COPD than asthma.

Aims of the Treatment of COPD

The goals of the therapy of COPD can be divided into four major aims:

1 Controlling symptoms and improving the quality of life.
2 Reducing future risk, that is preventing exacerbations.
3 Slowing down the progression of the disease.
4 Reducing mortality.

Multimodal Therapy of COPD

The therapy of COPD includes both non-pharmacological and pharmacological means. Non-pharmacological treatment modalities include smoking cessation [28], oxygen therapy, physical exercise and pulmonary rehabilitation, ventilator support and surgical therapy. Palliative care in patients nearing death is discussed in detail in the original document and may include a trial of opioids for refractory dyspnoea [2,9]. The risk of physical inactivity in patients with COPD is vastly increased (A) [29], and the patients should be encouraged to do physical exercise. Physical activity reduces the risk of mortality and hospitalizations. In contrast, physical inactivity predicts increased mortality (A) [30,31]. Exercise-based pulmonary rehabilitation courses should be available for COPD patients with continued dyspnoea despite the use of bronchodilators, or when they are physically inactive and suffer from frequent exacerbations, or have exercise intolerance. These recommendations can be found in detail in the original document [2,8,9]. Pharmacological therapies include bronchodilators, combinations of ICS and long-acting bronchodilators, phosphodiesterase 4 (PDE4) inhibitors or theophylline and influenza and pneumococcal vaccination.

Vaccination

In the general population, vaccination of persons aged >65 years against influenza has been found to reduce pneumonia, hospitalization and deaths by 50–68%. A majority of patients with COPD belong to this age group. Vaccination against influenza reduces COPD exacerbations (A) [32]. Vaccination annually against influenza is recommended for all patients with COPD.

Pneumococcal vaccination apparently reduces pneumonia of pneumococcal origin in patients with COPD (B) [33–35]. Pneumococcal vaccination is recommended for patients with COPD.

Pharmacotherapy of Stable COPD

Principles of regular long-term pharmacotherapy of COPD.

1 There exist two main goals with the current pharmacotherapy of COPD. They are (1) to control symptoms and (2) to reduce future risk (i.e. the exacerbations of COPD). The grounds for the use of any particular treatment in COPD may be either one of these goals or both goals together. The continuation or termination of a specific therapy is decided based on which goal is targeted (fig. 1).
2 If a particular pharmacotherapy is started in an effort to achieve both goals, the decision whether to continue or discontinue is made based on goal 2, that is the aim to reduce future risk (exacerbations). This is because the ability or inability of any particular drug to improve lung function or symptoms is not known to predict its ability to reduce exacerbations of COPD.
3 The pharmacological groups of inhaled drugs and the compounds used in the pharmacotherapy of COPD are shown in table 3.
4 The effects of several pharmacotherapies of COPD as well as the effects of smoking cessation and exercise on different end-points and goals in the treatment of COPD are shown in table 4.
5 The pharmacotherapy of COPD is based on the individual patient phenotype, on the level of symptoms and the risk of exacerbations. These are described in the section

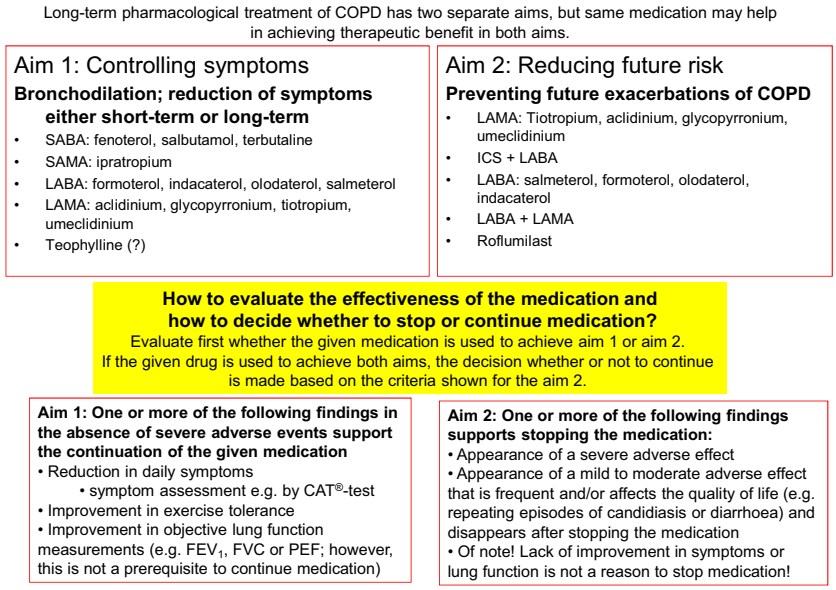

Fig. 1. Aims of the pharmacotherapy of chronic obstructive pulmonary disease (COPD) and principles for the evaluation whether to continue or discontinue the current medication.

'COPD phenotypes and phenotype-specific pharmacotherapy of COPD'. Grouping of patients to three different phenotypes is shown in fig. 2.

6 Phenotype and phenotype-based pharmacotherapy (fig. 2) should be evaluated at every visit to health care as the phenotype may change when the disease progresses (especially with regard to an increase in exacerbation risk) [36].

7 So far, no pharmacotherapy has definitively been shown to slow down disease progression (annual FEV_1 decline) or reduce mortality [37–43], even though preliminary findings suggesting such effects have been published.

8 The principles for combining different drugs in the treatment of COPD are shown in table 5.

9 A short-acting bronchodilator to be used on as-needed basis is considered beneficial for most patients treated with long-acting bronchodilators or combination therapy including long-acting bronchodilators.

Bronchodilators.

Drugs that relieve bronchial obstruction by reducing bronchial smooth muscle contraction are called bronchodilators. Usually, they improve spirometric values reflecting obstruction such as FEV_1. These compounds generally improve also emptying of the lungs and reduce air trapping (dynamic hyperinflation/restriction) both at rest and during exercise [44]. These effects cannot be predicted based on the ability of the particular compound to improve FEV_1 [45–48]. The dose–response effect of all bronchodilators at the currently used doses is relatively flat, which means that a small increase (e.g. doubling) in the dose is not expected to produce a vast increase in the bronchodilatory action [49–51]. The adverse effects are generally dose-related. Increase in the dose of short-acting inhaled β_2-agonist and anticholinergic, especially when given nebulized, may relieve subjective dyspnoea in acute setting during an exacerbation of COPD but may not help as a long-term therapy [52,53].

Bronchodilators can be divided into short acting (duration of bronchodilatory effect generally 3–6 hr) and long acting (duration of bronchodilatory effect generally 12–24 hr). There are two different classes of bronchodilators that have basically similar bronchodilatory action in the treatment of COPD but different mechanism of action. These pharmacological classes are β_2-agonists and muscarinic receptor (M_1, M_2 and M_3) antagonists (termed anticholinergics) [54,55]. Both of these pharmacological classes contain short-acting and long-acting preparations. Bronchodilators are usually administered on either as-needed (usually short-acting preparations) or regularly (usually long-acting preparations) to treat or prevent the occurrence of symptoms.

A short-acting bronchodilator to be used as-needed is considered beneficial for most patients even though they were treated with long-acting bronchodilators or combination therapy including long-acting bronchodilators. Instead, the use of regular, high-dose (nebulized, etc.), short-acting bronchodilator or their combination in patients treated with long-acting bronchodilators is not evidence based [3] and should only be reserved to treatment of the most difficult cases. In such a situation, the need for long-acting bronchodilators should be carefully evaluated as well as the ability of the patient to properly inhale them.

Short- and long-acting β_2-agonists (SABA, LABA).

The main beneficial effect of β_2-agonists is the reduction of bronchial smooth muscle contraction that leads to relief of bronchial obstruction. The duration of the effect of short-acting β_2-agonists is usually 3–6 hr. Short-acting β_2-agonist used either as-needed or regularly reduce symptoms of COPD and improve lung function [56]. The effect of long-acting β_2-

Table 3.
Pharmacological compounds used in the therapy of chronic obstructive pulmonary disease.

Pharmacological group and its abbreviation	Compounds belonging to the group
Short-acting β_2-agonists	Salbutamol
	Terbutaline
Long-acting β_2-agonist (LABA)	Formoterol
	Indacaterol
	Olodaterol
	Salmeterol
	Vilanterol
Short-acting anticholinergic	Ipratropium
Long-acting anticholinergic (LAMA)	Aclidinium
	Glycopyrronium
	Tiotropium
	Umeclidinium
Inhaled glucocorticoids (ICS)	Beclomethasone dipropionate
	Budesonide
	Ciclesonide
	Fluticasone propionate
	Fluticasone furoate
	Mometasone
Fixed combination of inhaled glucocorticoid and long-acting β_2-agonist (ICS + LABA)	Budesonide–formoterol
	Beclomethasone dipropionate–formoterol
	Fluticasone propionate–salmeterol
	Fluticasone furoate–vilanterol
Fixed combination of long-acting anticholinergic and long-acting β_2-agonist (LAMA + LABA)	Glycopyrronium–indacaterol
	Umeclidinium–vilanterol
Phosphodiesterase 4 (PDE4) inhibitors	Roflumilast
Others	Theophylline

agonists lasts 12 hr (formoterol or salmeterol) or 24 hr (indacaterol, olodaterol or vilanterol). The bronchodilatory action of formoterol/indacaterol/olodaterol/vilanterol starts sooner (within 5 min.) than that of salmeterol (within 20–30 min.). Indacaterol improves lung function (e.g. FEV_1), reduces dyspnoea during exercise and improves the quality of life, but the evidence on the reduction of COPD exacerbations is still preliminary [57–60]. The efficacy of indacaterol, olodaterol or vilanterol, when measured using FEV_1 or quality of life, is at least as good as that of formoterol or salmeterol [58,61–63] or the long-acting anticholinergic tiotropium [58,61,64].

Generally, β_2-agonists are well tolerated. Typical adverse effects include tremor, tachycardia and palpitations that have been reported in <1% of patients. Headache, muscular cramps and an increase in the blood glucose and a decrease in potassium levels are possible, even though these events occur almost as often in patients treated with placebo [65]. It has been suggested that activation of heart β_2-receptors by β_2-agonists might induce ischaemia, cardiac insufficiency and arrhythmias or increase the risk of sudden death. However, in controlled clinical studies recruiting patients with COPD, there is no indication for the increase of arrhythmias or cardiac deaths [65] or overall mortality [66] by β_2-agonists. Based on a case–control study [67], an increase in the risk of severe arrhythmias is possible. Thus, the benefits of using long-acting β_2-agonist in patients with severe cardiac disease should be carefully considered.

The use of long-acting β_2-agonists in the treatment of asthma in the absence of simultaneous ICS is prohibited [7] because there is evidence that treatment of asthma with long-acting β_2-agonists in the absence of ICS increases mortality due to asthma [68]. In contrast, in the treatment of COPD, a long-acting β_2-agonist can be used as the sole therapy as it does not increase mortality in COPD according to the studies published [65,66]. According to some cohort studies, use of long-acting β_2-agonist may even reduce the mortality of patients with COPD [69,70].

Short- and long-acting anticholinergics (SAMA, LAMA). Anticholinergic compounds block muscarinic receptors (M_1, M_2 and M_3), thus antagonizing acetylcholine-induced bronchial smooth muscle contraction. The duration of the effect of short-acting anticholinergic (ipratropium) is usually somewhat longer (even up to 8 hr) than that of the short-acting β_2-agonists (3–6 hr), but starts more slowly [54,55]. The effect of long-acting anticholinergics lasts either 12 hr (aclidinium) or approximately 24 hr (glycopyrronium, tiotropium or umeclidinium). Of these, tiotropium has been most extensively studied and used. The bronchodilatory action of aclidinium and glycopyrronium starts sooner than that of tiotropium.

Tiotropium improves lung function and quality of life and reduces symptoms and exacerbations of COPD (A) [71]. In contrast, tiotropium does not affect the progression of the disease as judged by the annual decline in FEV_1 [72]. Tiotropium may be more effective than salmeterol in reducing exacerbations of COPD [73]. Both aclidinium and glycopyrronium have been shown to induce bronchodilation, improve lung function and quality of life and reduce the need for rescue medication [74,75], and their efficacy roughly equals to that of tiotropium. Aclidinium, glycopyrronium and umeclidinium have been shown to reduce COPD exacerbations in studies lasting up to 1 year [76–78], but long-term studies lasting more than 1 year, similar to those made with tiotropium [72,73], are still lacking.

Inhaled anticholinergics are generally well tolerated, and adverse effects occur relatively seldom. Typical adverse effects, such as dry mouth, blurred vision, throat irritation, rhinitis, constipation and nausea, are due to blocking of muscarinic receptors. Other possible adverse effects include also arrhythmias, urinary retention/obstruction, elevated intraocular pressure and acute or worsening of narrow-angle glaucoma [79].

The short-acting anticholinergic ipratropium has been suspected to induce cardiac adverse effects [79]. With the long-acting anticholinergics, no similar increase in cardiac adverse effects has been reported with certainty [79]. The 4-year-long UPLIFT trial reported that there were statistically significantly less cardiac adverse effects and the total mortality was numerically, although not statistically, lower in patients treated with tiotropium [72].

Recently, it has been proposed that dosing of tiotropium with Respimat® device (Boehringer Ingelheim, Ingelheim,

Table 4.
Effects of smoking cessation, exercise and various pharmacotherapies in the treatment of chronic obstructive pulmonary disease (COPD).

	Smoking cessation	Exercise	Short-acting bronchodilator (β_2-agonist or anticholinergic)	Long-acting β_2-agonist	Long-acting anticholinergic	Addition of inhaled glucocorticoid in severe COPD[1]	Roflumilast in severe COPD
Symptoms	+	+	+	+	+	(+)	–
Obstruction	+	–	+	+	+	(+)	(+)
Exacerbations	+	+	–	+	+	+	+
Disease progression (annual FEV_1 decline)	+	?	–	–	–	(+)	?
Mortality	+	+	–	–	–	(+)	?

+: definite beneficial effect; (+): small or possible beneficial effect; –: no effect; ?: no evidence.
[1]In practice means terminating long-acting β_2-agonist and prescribing a combination product containing both inhaled glucocorticoid and long-acting β_2-agonist.

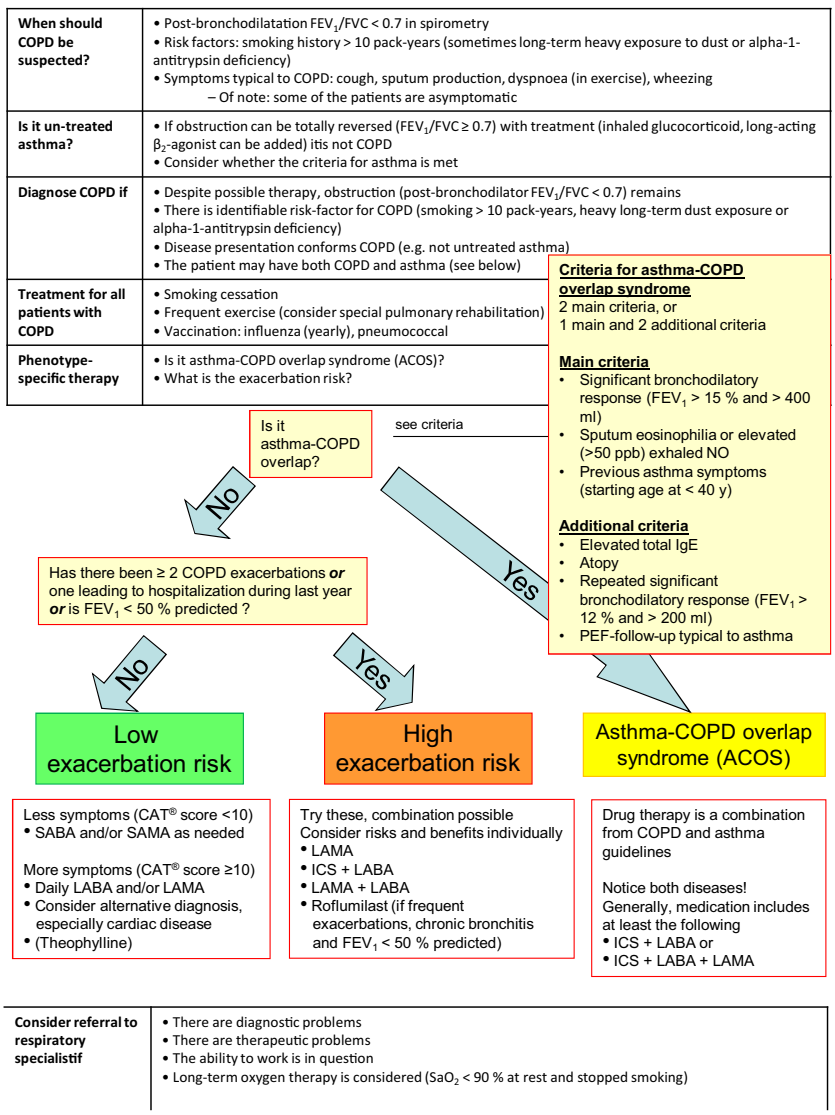

Fig. 2. The principles of diagnostics and phenotype-specific therapy of chronic obstructive pulmonary disease (COPD). Of note, the current indication for the use of different fixed combinations of inhaled glucocorticoid ICS and long-acting β_2-agonist (LABA) in COPD is frequent exacerbations despite the use of appropriate bronchodilator therapy, but the FEV_1 ranges from <50% predicted (budesonide–formoterol, beclomethasone dipropionate–formoterol) to <60% predicted (fluticasone propionate–salmeterol) and to <70% predicted (fluticasone furoate–vilanterol).

Table 5.

The principles of combining drugs used to treat chronic obstructive pulmonary disease (COPD). The general rule of drug therapy of COPD is that two drugs belonging to the same group or having similar mechanism of action should not be combined. The exception to this rule is the simultaneous use of short- and long-acting β_2-agonists that is allowed and often is meaningful.

If there is a clinical indication to combine drugs from the following groups, there is no pharmacological reason to prevent the combination. To a single patient, only one compound or product can be selected from the following groups of drugs
Short-acting bronchodilators ('reliever medication')[1]
Short-acting β_2-agonist (fenoterol, salbutamol, terbutaline)
Short-acting anticholinergic (ipratropium)[2]
Long-acting bronchodilators[1]
Long-acting β_2-agonist (formoterol, indacaterol, olodaterol, salmeterol, vilanterol)
Long-acting anticholinergic (aclidinium, glycopyrronium, tiotropium, umeclidinium)[2]
Glucocorticoids
Inhaled glucocorticoids (beclomethasone, budesonide, fluticasone, mometasone, ciclesonide)
Oral medications
Phosphodiesterase 4 inhibitors (roflumilast)[3]
Theophylline[3]

[1]The duration of action of the compound does not prevent the combination. For example, two long-acting bronchodilators can be combined as long as they have a different mechanism of action (i.e. tiotropium and indacaterol can be combined). Similarly, short-acting anticholinergic (ipratropium) can be combined with short-acting β_2-agonist (e.g. salbutamol). Instead, two different β_2-agonists with similar duration of action should not be combined (e.g. indacaterol should not be combined with formoterol or salmeterol). Use of a short-acting β_2-agonist as needed with a regular long-acting β_2-agonist is acceptable.

[2]Use of short-acting anticholinergic (ipratropium) with long-acting anticholinergic is not recommended.

[3]Phosphodiesterase 4 inhibitors and theophylline should not be combined because of the risk of adverse effects.

Germany) would cause more deaths than its dosing with Handihaler® device (Boehringer Ingelheim, Ingelheim, Germany) [79]. However, a direct comparison of the two devices for a mean of 2.3 years indicated that there were no differences in mortality, serious cardiac adverse effects or exacerbations of COPD [80].

Combination bronchodilator therapy.

Bronchodilators with a different mechanism or duration of action can be relatively freely combined (table 5), and the combination may have a better bronchodilatory effect [81]. For example, combination of a short-acting anticholinergic with a short- or long-acting β_2-agonist improves FEV_1 better than any of the single agents [81,82]. Short- or long-acting β_2-agonist can be combined with a long-acting anticholinergic if a single agent is not improving symptoms enough [81–83]. The combination of tiotropium and a long-acting β_2-agonist apparently improves the lung function and quality of life somewhat better than tiotropium alone (B) [83]. The use of short- and long-acting anticholinergic compounds together is not recommended. Even though this combination may improve results of lung function tests better than the single agents, it will increase the risk of adverse effects such as urinary retention [84]. Combination of a short-acting β_2-agonist with a long-acting anticholinergic will result in at least as good a response in lung function parameters without a risk of anticholinergic adverse effects. Thus, if a patient is using a long-acting anticholinergic, the rescue medication should be a short-acting β_2-agonist [84].

After the finalization of the Finnish guideline [2,8,9], two fixed-dose combinations of a long-acting β_2-agonist and a long-acting anticholinergic have been approved to be used in the treatment of COPD, namely indacaterol–glycopyrronium and vilanterol–umeclidinium. In most studies, both of these fixed combinations have been shown to improve lung function (e.g. trough FEV_1) and health status and to reduce dyspnoea better than the single monocomponents alone in patients with moderate-to-severe COPD with no apparent safety concerns [64,85–89]. In addition, the fixed-dose combination of indacaterol–glycopyrronium has been reported to reduce moderate-to-severe COPD exacerbations better than glycopyrronium alone [90].

Inhaled glucocorticoids.

In the treatment of asthma, the therapeutic and adverse effects of ICS depend on the dose used [91]. Instead, in the treatment of COPD, the dose dependency of the therapeutic and adverse effects of ICS is not known [92,93]. In long-term trials, only moderate and high doses of ICS have been used [92,93]. Regular long-term (>6 months) therapy with ICS in COPD reduces exacerbations and slows down the decline in the quality of life [93]. Generally, patients with mild disease and without previous exacerbation history do not benefit from ICS [3,93]. The response to ICS in COPD cannot be foretold from the response to oral glucocorticoids or by measuring hyperreactivity or response to bronchodilators (bronchodilator test in spirometry) [93]. Discontinuation of ICS may precipitate exacerbation of the disease in some patients with COPD [94] but may be safely performed in others to decrease risk of long-term adverse effects [95]. ICS alone do not affect mortality due to COPD or the rate of decline of lung function (annual FEV_1 decline) [93]. Adverse effects include candida infection in the mouth and hoarseness. Also, there is evidence that use of ICS is associated with an increased risk of pneumonia [93] and fractures [96]. Initiation of ICS therapy has been associated with increased risk of diabetes in respiratory

patients in general in a registry-based study [97], but in a retrospective analysis of shorter placebo-controlled, double-blind studies in patients with asthma or COPD, it has not been confirmed [98].

Long-term therapy with ICS in addition to other therapy is recommended only for patients with ACOS or patients with a high risk of exacerbations of COPD, that is with severe or very severe obstruction in spirometry (table 2) and a history of frequent exacerbations (fig. 2) [99]. The use of ICS as the sole long-term therapy of COPD should be avoided as the combination of inhaled glucocorticoid with long-acting β_2-agonist is more efficient in reducing exacerbations of the disease and possibly better in reducing mortality and improving lung function and quality of life [100]. The use of ICS outside the current indications is not recommended as long-term therapy with these may increase the risk of pneumonia [92,93], osteoporosis and fractures [96].

Combination of inhaled glucocorticoid and long-acting β_2-agonist.

In COPD, the current indication for the use of different fixed combinations of ICS and long-acting β_2-agonist is frequent exacerbations despite the use of appropriate bronchodilator therapy, but the accepted FEV_1 ranges from <50% predicted (budesonide–formoterol, beclomethasone dipropionate–formoterol) to <60% predicted (fluticasone propionate–salmeterol) and to <70% predicted (fluticasone furoate–vilanterol). The combination of inhaled glucocorticoid and a long-acting β_2-agonist reduces exacerbations and improves lung function and quality of life in COPD (A) [101]. In addition, combination of inhaled glucocorticoid and a long-acting β_2-agonist is better than placebo or any of its components in improving lung function and health status and reducing exacerbations in patients with COPD [100,102–105]. In a large, prospective 3-year trial with a combination of inhaled glucocorticoid and a long-acting β_2-agonist, there was no statistically significant effect on mortality [106]. However, in a subsequent meta-analysis, it was found that a combination of inhaled glucocorticoid and a long-acting β_2-agonist may reduce mortality (number needed to treat NNT = 36 to prevent one extra death; 95% CI 21; 258) [104].

The use of a combination of an inhaled glucocorticoid and a long-acting β_2-agonist is associated with adverse effects typical for both its components. The increased risk of pneumonia is considered as the most significant in patients with COPD [99,104]. At present, it remains uncertain to what extent increased risk of pneumonia is associated with other ICS or combinations of ICS and long-acting β_2-agonists, but a combination of inhaled fluticasone propionate and salmeterol may cause a higher risk [107–110].

Even though COPD is largely an under-diagnosed and under-treated disease [3], over-treatment of mild-to-moderate COPD (spirometric GOLD classification; table 2) with combinations of ICS and long-acting β_2-agonists was recently reported [111]. This cannot be recommended and leads to unnecessary adverse effects and costs [111].

Addition of a combination of an inhaled glucocorticoid and a long-acting β_2-agonist to tiotropium therapy has been reported to improve lung function and the quality of life, and it may even further reduce the occurrence of exacerbations, particularly severe exacerbations [112–115], but more and longer studies are needed. Preliminary evidence suggests that the triple therapy is cost-effective in Finland and other Scandinavian countries [116].

Roflumilast.

Roflumilast inhibits the inflammatory reaction associated with COPD by inhibiting enzyme phosphodiesterase 4 (PDE4) and by increasing intracellular cyclic adenosine monophosphate (cAMP) content [57]. Roflumilast is given orally as one tablet daily. It is not a bronchodilator and cannot be used to relieve acute bronchial obstruction, even though during long-term therapy in patients already on salmeterol or tiotropium, roflumilast further increases FEV_1 by 50–80 ml [57,117–119].

Roflumilast reduces exacerbations of COPD and improves lung function, but it also has significant adverse effects (A) [117]. Roflumilast reduces moderate (requiring systemic glucocorticoids) and severe (leading to hospitalization or death) exacerbations in patients with COPD who have severe COPD (FEV_1 < 50% predicted), chronic bronchitis and frequent exacerbations despite long-acting bronchodilators [57,117,118]. In contrast, the effects on the quality of life and symptoms are less pronounced [57,117].

Typical adverse effects of roflumilast are gastrointestinal complaints and headache. Weight loss is also common, and the weight should be followed [117,118].

Other pharmacological treatments used for long-term therapy.

Oral glucocorticoids. A treatment trial with oral glucocorticoids is not recommended in patients with COPD to identify those who will respond to ICS. A response to oral glucocorticoids has not been shown to predict the response to other treatments [23–27]. However, this does not prevent us from treating exacerbations with a course of oral steroids or trying a course of oral steroids in a patient with difficult symptoms.

Even though a high dose (equalling ≥30 mg oral prednisolone per day) of oral glucocorticoids improves lung function in the short run, there is no evidence of long-term benefits of oral glucocorticoids at low or moderate to high doses [120]. In contrast, there is evidence to suggest increased risk of adverse effects [120]. Thus, long-term therapy of COPD with oral glucocorticoids should be avoided as it may even worsen the long-term outcome of the patient [121]. Oral glucocorticoids have several significant adverse effects – one of the most important in the treatment of COPD being steroid myopathy which presents with symptoms such as muscular weakness, impaired physical activity and respiratory insufficiency in patients with very severe COPD [122]. Regular long-term oral glucocorticoid therapy has several well-known adverse effects, and thus, it is easy to understand that there exist no studies on its use in the treatment of stable COPD [3].

Theophylline. The exact mechanism of action of theophylline remains unknown, but it has both bronchodilatory and anti-inflammatory effects. The pharmacokinetics of theophylline varies between individuals and is prone to drug–drug interactions [123,124]. For this reason, its blood concentrations need to be followed and the dosing needs to be adjusted. The duration of effect in COPD is not known even in the case of currently used slow-release preparations [3].

The reports on the effects of theophylline in COPD are controversial. Theophylline apparently improves lung function in COPD, but the risk of adverse effects increases (B) [125–127]. Theophylline may improve the function of inspiratory muscles [123]. The effect of theophylline on lung function and symptoms in COPD is less than that of long-acting β_2-agonists formoterol and salmeterol [126,128]. Addition of theophylline to salmeterol improved FEV_1 and reduced dyspnoea better than salmeterol alone [128]. Small dose of theophylline (100 mg twice daily) reduced COPD exacerbations statistically significantly, but did not improve lung function as judged by post-bronchodilator spirometry [127].

The therapeutic concentration range of theophylline is narrow, and widespread toxicity is easily a problem [3,123,124]. The most usual adverse effects include gastric irritation, nausea, vomiting, diarrhoea, increased diuresis and signs of stimulation of central nervous (headache, nervousness, anxiety and agitation) and cardiac electrical (arrhythmias, specially tachycardia) systems [54,55,123,124,129]. For this reason, the use of theophylline has diminished, and it is recommended for the treatment of COPD only as an additional therapy to patients with severe symptoms.

Antimicrobial compounds.

A recent meta-analysis reported that regular use of macrolides (erythromycin, clarithromycin and azithromycin) in six studies (lasting 3–12 months) resulted in a 37% decrease in COPD exacerbations as compared with placebo. In addition, hospitalization was reduced by 21%, and the share of patients suffering from exacerbations was reduced by 68% but at the expense of increased risk of hearing loss [130,131]. However, a widespread use of macrolides is restrained by the fear of increased resistance of bacteria to macrolides [130].

Compounds affecting sputum production or consistency (mucolytics).

The group of mucolytic drugs consists of several compounds with varied mechanisms of actions, part of which remain unknown [54,55]. The regular use of mucolytics in COPD has been a subject of several studies with conflicting results [3,132].

Mucolytics apparently reduce COPD exacerbations, but they do not improve lung function or induce significant adverse effects (B) [132].

Choice of the inhaler.

A significant proportion of the patients commit errors in using their inhalers [133], so the correct use should be taught and controlled when starting the treatment and also at control visits.

The use of dry powder inhaler (DPI) does not require co-ordination of actuating the device and inhalation, but sufficient inspiratory strength is needed to create high enough inspiratory flow.

The use of pressurized, metered dose inhaler (pMDI) does not require high inspiratory flow, but the patient needs to be able to co-ordinate the actuation of the inhaler at the beginning of inhalation.

The use of valved holding chambers or spacer devices alleviates the problem with co-ordination, and they diminish oral and pharyngeal deposition when suspension aerosols are used [134].

Inspiratory flow is not always sufficient for the use of DPI in individuals with a more severe COPD [135]. A pMDI should then be used, and, if needed, holding chamber with or without mask and assistance from a caregiver can also be used. The basic principles of choosing a correct inhaler are shown in table 6 [136].

COPD Phenotypes and Phenotype-Specific Pharmacotherapy of COPD

1 The pharmacotherapy of COPD is based on the individual patient phenotype, on the level of symptoms and the risk of exacerbations. Grouping of patients to three different phenotypes is shown in fig. 2.

Table 6.

Choosing a suitable inhaler.

Choosing a suitable inhaler 1. Assess the patients' ability to co-ordinate actuation of the pMDI and inhalation 2. Assess the patients' ability to create sufficient inspiratory flow for using DPI			
Good co-ordination		Poor co-ordination	
Inspiratory flow > 30 l/min.	Inspiratory flow < 30 l/min.	Inspiratory flow > 30 l/min.	Inspiratory flow < 30 l/min.
DPI pMDI SMI BA-MDI (nebulizer)	pMDI SMI (nebulizer)	DPI BA-MDI pMDI + spacer (SMI) (nebulizer)	pMDI + spacer (SMI) (nebulizer)

DPI, dry powder inhaler; pMDI, pressurized, metered dose inhaler; SMI, soft mist inhaler; BA-MDI, breath-actuated metered dose inhaler.
Modified from reference [136].

2 Phenotype and phenotype-based pharmacotherapy (fig. 2) should be evaluated at every health care visit as the phenotype may change when the disease progresses (especially with regard to exacerbation risk) [36].

Low risk of exacerbations.

A phenotype of COPD that is characterized by a low risk of exacerbations based on infrequent previous exacerbations and relatively good lung function (i.e. $FEV_1 \geq 50\%$ predicted) and the patient is not presenting with the typical features of ACOS (fig. 2). The patients are divided into two groups: those with less symptoms (CAT® score < 10 or mMRC score < 2) or those with more symptoms (CAT® score ≥ 10 or mMRC score ≥ 2 points) and limitations of physical activity or quality of life due to COPD.

1 In patients with less symptoms, a short-acting bronchodilator, either β_2-agonist or anticholinergic, is recommended. If a single compound is not enough to control the symptoms, a combination of short-acting β_2-agonist and anticholinergic can be used, even though there is not much evidence to support this treatment option [81].

2 If a short-acting bronchodilator is not enough to control the symptoms or the patient is having plenty of symptoms, a long-acting bronchodilator, either β_2-agonist or anticholinergic, can be used. In patients with more symptoms, long-acting bronchodilators are more effective than short-acting bronchodilators and thus are recommended [82,137].

3 At the moment, there is not enough evidence available to recommend one class (β_2-agonist or anticholinergic) of long-acting bronchodilators over the other as initial therapy in COPD [3]. The choice of a long-acting bronchodilator for long-term use should be made based on the symptomatic benefit experienced by the patient.

4 A combination of tiotropium and a long-acting β_2-agonist apparently improves the quality of life and lung function better than tiotropium alone (B) [58,83].

5 A combination product of long-acting bronchodilators (glycopyrronium and indacaterol) apparently improves spirometric lung function test results and quality of life better than any of its components alone (B) [85,90].

6 Theophylline can be combined to the bronchodilators described above, but the evidence to recommend its use alone or as a combination is limited. Theophylline apparently improves lung function in COPD, but the risk of adverse effects increases (B) [125–127].

7 If the patient is experiencing more symptoms and his/her lung function is only moderately reduced (i.e. FEV_1 is ≥50% predicted), then consider the possibility of additional or alternative diagnosis, especially cardiac disease or lung cancer [36,138].

High risk of exacerbations.

A phenotype that is characterized by a high risk of exacerbations either based on previous exacerbation history or severe to very severe airflow limitation (i.e. FEV_1 is <50% predicted) and the patient is not presenting with the typical features of ACOS. The main aim of the pharmacotherapy in this patient group in addition to relieving symptoms is to prevent and to reduce the severity of exacerbations of COPD.

The recommended first choice of pharmacotherapy is as follows:

1 A long-acting anticholinergic or a combination of inhaled glucocorticoid and long-acting β_2-agonist:

- The combination of inhaled glucocorticoid and a long-acting β_2-agonist reduces exacerbations and improves lung function and quality of life in COPD (A) [101].
- Tiotropium improves lung function and quality of life and reduces symptoms and exacerbations of COPD (A) [71].
- There is not enough evidence available to recommend one of these options over the other as initial therapy in high exacerbation risk phenotype of COPD [139].

Other treatment options:

1 Combination of two long-acting bronchodilators:

- Long-acting anticholinergics [71] and long-acting β_2-agonists [140] reduce exacerbations of COPD, even though studies evaluating the effects of a combination of long-acting bronchodilators administered via separate inhalers are still scarce [58,83].
- A combination product of long-acting bronchodilators (glycopyrronium and indacaterol) apparently improves spirometric lung function test results and quality of life better than its components alone (B) [85,90] and may reduce COPD exacerbations better than long-acting anticholinergic alone [90] and thus may be used.

2 Roflumilast:

- If the patient is having severe-to-very severe COPD ($FEV_1 < 50\%$ predicted), chronic bronchitis and frequent exacerbations despite long-acting bronchodilators, the pharmacotherapy may include also roflumilast.
- Roflumilast reduces exacerbations of COPD and improves lung function, but it also has significant adverse effects (A) [117].

3 Triple therapy:

- If the patient is having more symptoms in addition to exacerbations, a combination of three agents (i.e. an inhaled glucocorticoid, a long-acting β_2-agonist and a long-acting anticholinergic) may be used. The evidence of the usefulness of this triple combination is mainly based on short trials [112–115].

4 Inhaled glucocorticoid and long-acting anticholinergic:

- This is not a therapy based on strong evidence, but in theory it is considered sensible. The reason for the absence of evidence most probably is due to the lack of interest by the pharmaceutical industry rather than not being a rational combination [3].

5 Long-acting β_2-agonist:

- Long-acting β_2-agonist (formoterol or salmeterol) reduces exacerbations and hospitalizations due to COPD and improves lung function (A) [106,140,141]. Both com-

pounds also improve significantly the quality of life and reduce the need for rescue medication, but do not reduce mortality due to COPD or the annual decline in FEV_1 [106,140].

• Long-acting β_2-agonist as the sole therapy of high-risk phenotype of COPD is not, however, recommended because these studies were not carried out in patients prone to COPD exacerbations [140] and because there is solid evidence of the efficacy of both the long-acting anticholinergic [71] and the combination of inhaled glucocorticoid and long-acting β_2-agonist [104] in this indication.

6 Theophylline:

• Theophylline can be combined with inhaled glucocorticoid and/or long-acting bronchodilators, but the evidence of its efficacy in reducing COPD exacerbations as part of a combination therapy or alone is very limited [127]

7 Antibiotics

• Regular use of macrolides (erythromycin, clarithromycin and azithromycin) reduces COPD exacerbations [130], but widespread use of macrolides is restrained by the fear of increased resistance of bacteria to macrolides. For this reason, long-term therapy with antimicrobial compounds should be restricted to patients who suffer from repeated exacerbations leading to hospitalization despite adequate pharmacotherapy of COPD [92]. The decision to start and to follow up on this kind of therapy always necessitates specialist consultation.

8 Compounds affecting sputum production or consistency (mucolytics)

• Mucolytics apparently reduce COPD exacerbations, but they do not improve lung function or induce significant adverse effects (B) [132].

• The long-term use of mucolytics in the routine therapy of COPD is not recommended. However, some patients presenting with severe over-production of viscous mucus may benefit from them [132]. At the moment, no clear evidence exists to guide the use of mucolytics in COPD (i.e. which compound, to which kind of patients and for how long).

Asthma–COPD overlap syndrome.

1 This is a phenotype of COPD in which there are features that comply both with asthma and with COPD (fig. 2). Patients belonging to this phenotype have been usually excluded from studies evaluating the effects of drugs both in asthma and in COPD [142–144]. Thus, evidence-based recommendation of treatment cannot be given. Furthermore, there exist no generally accepted criteria for this condition [6,142].

2 In patients fulfilling the criteria for both asthma and COPD and who were using ICS, addition of tiotropium improved lung function test results and reduced the need for rescue medication [145].

3 The treatment should cover both diseases, and, generally, the therapy includes at least ICS combined with long-acting bronchodilator (β_2-agonist or anticholinergic or both) (the reader is strongly advised to familiarize him-/herself also with the Asthma guidelines) [6,7].

Conclusion

Optimal therapy of patients with COPD requires a tailored and multidisciplinary approach focusing on the symptoms and the individual future risk of the patient [3,4,146,147]. In addition, the personal needs and wishes should be taken into account [3–5,146]. The current guideline emphasizes early diagnosis with structured evaluation of the phenotype of each patient. The therapy should be started early in the course of the disease and should be phenotype-directed. The phenotype may change during the course of the disease and should be re-evaluated during each follow-up visit, and the pharmacotherapy should be changed according to the changed phenotype of the disease.

The paradigm shift in the treatment of COPD initiated by the GOLD (Global Initiative for Chronic Obstructive Lung Disease) report [3] offers a basis for the assessment of the future risk of the individual patient. However, at the same time, there is a huge lack of knowledge on the effects of pharmacotherapies on the symptoms and risks of different phenotypes of COPD as well as on patients with different comorbidities. Future studies with drugs directed towards COPD should take into consideration the different phenotypes of the disease and include patients with comorbidities and also follow-up for future risk end-points such as exacerbations, hospitalizations and mortality.

We recognize several limitations of the present guideline, and the reader may identify several deficiencies in the recommendations as well as topics that remain undiscussed. Several topics that were raised by the reviewers of the original Finnish guideline [2,8] as well as the present version in the English language remain untouched due to lack of evidence or due to very conflicting evidence. In fact, much more evidence is needed to evaluate the effectiveness of different therapies in COPD and its specific phenotypes. However, we have very little evidence that a specific pharmacotherapy would not help in COPD. Thus, the reader should not consider the 'lack of evidence that a treatment works' as a synonym for 'evidence that a specific treatment does not help' in COPD [3].

Limitation of responsibility.

The practice guidelines of the Finnish Medical Society Duodecim are summaries on the diagnostics and effectiveness of therapy on single diseases and are produced by experts. They do not replace the judgement of a physician or other healthcare specialist on the best possible diagnostics and therapy of an individual patient.

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