




Towards Rational Prescription of Common Inhaler Medication in the Multimorbid COPD Patient

Ioanna Tsiligianni¹


Kristian Jong Hoeines²

Christian Jensen ³

Janwillem WH Kocks ⁴⁻⁶

Björn Ställberg ⁷

Claudia Vicente⁸

Rudi Peché ⁹

¹Department of Social Medicine, University of Crete, Heraklion, Greece;

²Tananger Legesenter DA, Sola, Norway;

³Lægehuset Remisen, Præstø, Denmark;

⁴General Practitioners Research Institute, Groningen, the Netherlands; ⁵University of Groningen, University Medical Center Groningen, GRIAC Research Institute, Groningen, the Netherlands;

⁶Observational and Pragmatic Research Institute, Singapore; ⁷Department of Public Health and Caring Sciences, Family Medicine and Preventive Medicine, Uppsala University, Uppsala, Sweden;

⁸Unidade Saúde Familiar Araceti, Arazede, Portugal; ⁹Department of Pneumology, ISPPC, CHU Charleroi, Charleroi, Belgium

Abstract: COPD is a chronic disease, typically accompanied by multiple comorbid conditions. The need to apply several, and sometimes conflicting, disease-specific treatment guidelines, complicates the management of individual patients. Moreover, national and international recommendations evolve rapidly but provide limited guidance on the integrated approach in the multimorbid patient. Particularly bothersome is the fact that the presence of comorbidities may deteriorate the course of COPD, and inversely COPD may affect the outcome of the comorbid diseases. In addition, some effects of commonly prescribed COPD inhaler medications, including beta₂-agonists, long-acting antimuscarinics and especially inhaled corticosteroids, mimic or worsen COPD-related comorbidities. Therefore, the authors combined their perspectives to formulate advice that may help physicians to improve COPD patient care in daily practice when comorbidities are present. Diabetes, atrial fibrillation, osteoporosis/fractures, infections (pneumonia and tuberculosis) and asthma were identified as areas where practicing clinicians should give special attention to the risk-benefit ratio of the inhaled medication. Overall, the presence of multimorbidity in a COPD patient should act as a signal to carefully reconsider the treatment choices.

Keywords: comorbidity, multimorbidity, polypharmacy, inhaler medication

Introduction

In the rapidly aging population with increasing longevity, responsibilities of physicians are shifting towards the management of chronic diseases. These chronic diseases often appear in clusters due to common risk factors (eg, COPD and lung cancer), shared pathobiological mechanisms (eg, accelerated ageing in COPD and hypertension) and side effects of COPD treatment (eg, development of diabetes).^{1,2} The majority of consultations nowadays involve patients with many coexisting chronic conditions, while particularly in primary care, the workload to apply practice guidelines increases steeply with increasing numbers of concomitant illnesses.^{3,4} Bringing treatment guidelines into practice is not easy because international and national recommendations may vary substantially, and local regulations are often misaligned with the rapidly evolving treatment recommendations.⁵ Healthcare delivery gets particularly complicated when entering the world of multimorbidity, where single disease-specific guidelines must be combined to treat individual patients.⁶ Rarely do these guidelines provide clear direction on multimorbidity, not even in patients with only two simultaneous diseases.⁷

Correspondence: Ioanna Tsiligianni
Department of Social Medicine,
University of Crete, Voutes Campus,
Heraklion, Crete, 71003, Greece
Tel +30 2810394607
Email i.tsiligianni@uoc.gr

In patients with COPD, multimorbidity and the associated risk of hospitalization and premature death are highly prevalent, including also a high level of polypharmacy and potential adverse drug reactions.^{1,5,8–12} For the treating physician, COPD is one out of the many chronic diseases to account for, while symptoms and signs are usually complex and attributable to several causes.¹³ Patients themselves, struggling with smoking addiction and shame about self-inflicted disease, rarely seek medical help for their respiratory problems outside acute situations.¹⁴ Also, due to the progressive course of COPD, patients become used to the symptoms, not valuing them as they should. An all-inclusive consultation approach with sufficient time devoted to COPD, is essential.^{15,16} Such a holistic approach should include theory-driven patient assessment models to facilitate smoking cessation, patient empowerment, programs for physical activity, physiotherapy, rehabilitation as well as raising adherence to treatment and limiting unnecessary pharmaceutical treatment.

This paper brings a fresh perspective on the management of the poly-medicated multimorbid COPD patient. Our objective is to assess and describe the impact of inhalation medication, including beta₂-agonists (LABA), long-acting muscarinic antagonists (LAMA) and inhaled corticosteroids (ICS), as potential contributing factors to comorbid disease in COPD and formulate advice to enhance management of comorbid COPD patients.

How Common is Multimorbidity in COPD and What are the Challenges?

Most patients with COPD have a large number of long-term comorbidities, which affect their health outcomes and increase the risk of hospitalization and mortality.¹⁷ Importantly, COPD itself is also known to adversely influence the course of other conditions.¹³ The diagnosis of COPD tends to precede other comorbid conditions, at least in patients over 65 years of age.¹⁸ Concomitant diseases can also be overlooked because signs and symptoms overlap.

Up to 80% of patients with COPD suffer from at least one comorbid condition of clinical relevance; half of them have three or more.¹⁹ Comorbid conditions are even more frequent in women than men, and the prevalence increases with worsening COPD severity.^{19,20}

Comorbidities often appear in clusters, which can be explained by common risk factors (eg, smoking,

inactivity), shared underlying pathobiological mechanisms (eg, accelerated ageing), and the occurrence of side effects of COPD medication.^{1,2,21}

Common comorbidities in patients with stable COPD include cardiovascular diseases (heart failure, ischemic heart disease, arrhythmias, peripheral vascular disease, hypertension), asthma, skeletal muscle dysfunction, osteoporosis, anxiety and depression, lung cancer, metabolic syndrome, diabetes, gastroesophageal reflux, bronchiectasis, and obstructive sleep apnea.^{13,21} Figure 1 (panel A) provides a graphical representation of the comorbidities found in large European studies.^{10,22–28} The analysis underlying this figure can be found in the [Supplementary Data](#). The American Truven health database found that the most common comorbidities, ie, cardiovascular disease (35%), diabetes (23%), asthma (15%), anemia (14%), chronic kidney disease (10%), depression (10%), and osteoporosis (7%), all highly contribute to morbidity and use of health care resources.²⁹ The Swedish large, real-world, retrospective cohort, ARCTIC, which specifically examined patients from the primary care setting, showed significantly higher prevalence rates of lung cancer, heart failure, ischemic heart disease, hypertension, depression/anxiety, sleep disorders, osteoporosis, stroke, osteoarthritis, and pulmonary embolism in the COPD population compared with the non-COPD population in primary care.²⁵ Comorbidities also increased the occurrence of severe exacerbations in these COPD patients. Westerik et al calculated in their retrospective cohort study of more than fourteen thousand COPD patients from general practice in the Netherlands, that several comorbidities were significantly associated with an exacerbation frequency of ≥ 2 exacerbations/year, ie, heart failure, blindness and low vision, pulmonary cancer, depression, prostate disorders, asthma, osteoporosis, diabetes, dyspepsia and peripheral vascular disease.²⁶

Evolving Treatment Guidelines

While multimorbidity is omnipresent in daily clinical practice, the approach in clinical research is usually single disease-oriented, avoiding concomitant diseases via stringent study exclusion criteria or not reporting concomitant conditions. There is a clear need for more pragmatic studies that tackle complexity.¹³

GOLD has been a pioneer in this regard and, since a few years; has integrated the issue of multimorbidity in its reports, highlighting the importance of comorbidity

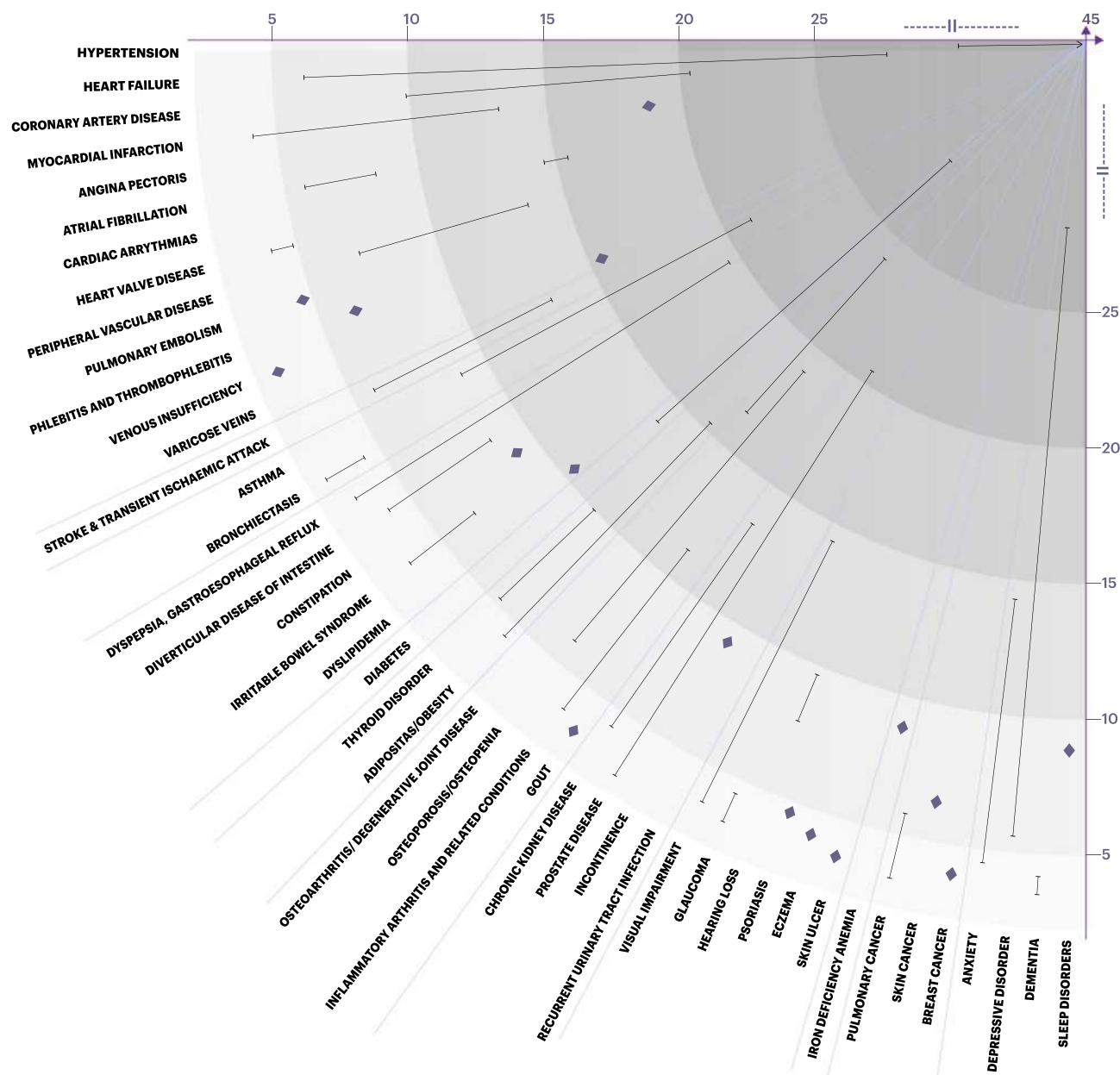


Figure 1 (A) Prevalence of frequent comorbid conditions (panel A)*. *Graphical representation of the comorbidities found in 6 large European studies (see Supplementary Data); lines (l–l) connect the minimal and maximal prevalence rates found in these studies; diamonds (◆) are used when the condition is reported in only one study.

assessment.¹³ Extrapolation into local practice guidelines remains scarce.

The current GOLD update (2021) has once more confirmed the central role of bronchodilation in the treatment of stable COPD.¹³ Inhaled bronchodilators are given on a regular basis to prevent or reduce symptoms, mainly breathlessness. The GOLD recommendations indicate that patients may be started on single or dual long-acting bronchodilator therapy. In patients with persistent dyspnea or exercise limitation on one bronchodilator, escalation to

two bronchodilators is advised. In patients with persistent exacerbations despite dual bronchodilator treatment, blood eosinophil counts may identify patients with a greater likelihood of a beneficial response to adding ICS.¹³ Depending on the population and severity of COPD, this group of frequent exacerbators, with 2 or more exacerbations in the previous years, varies widely in the literature with estimates up to 38%.^{30–36} The SPIROMICS study collected data on a general COPD population and found that persistent exacerbators with two or more acute exacerbations

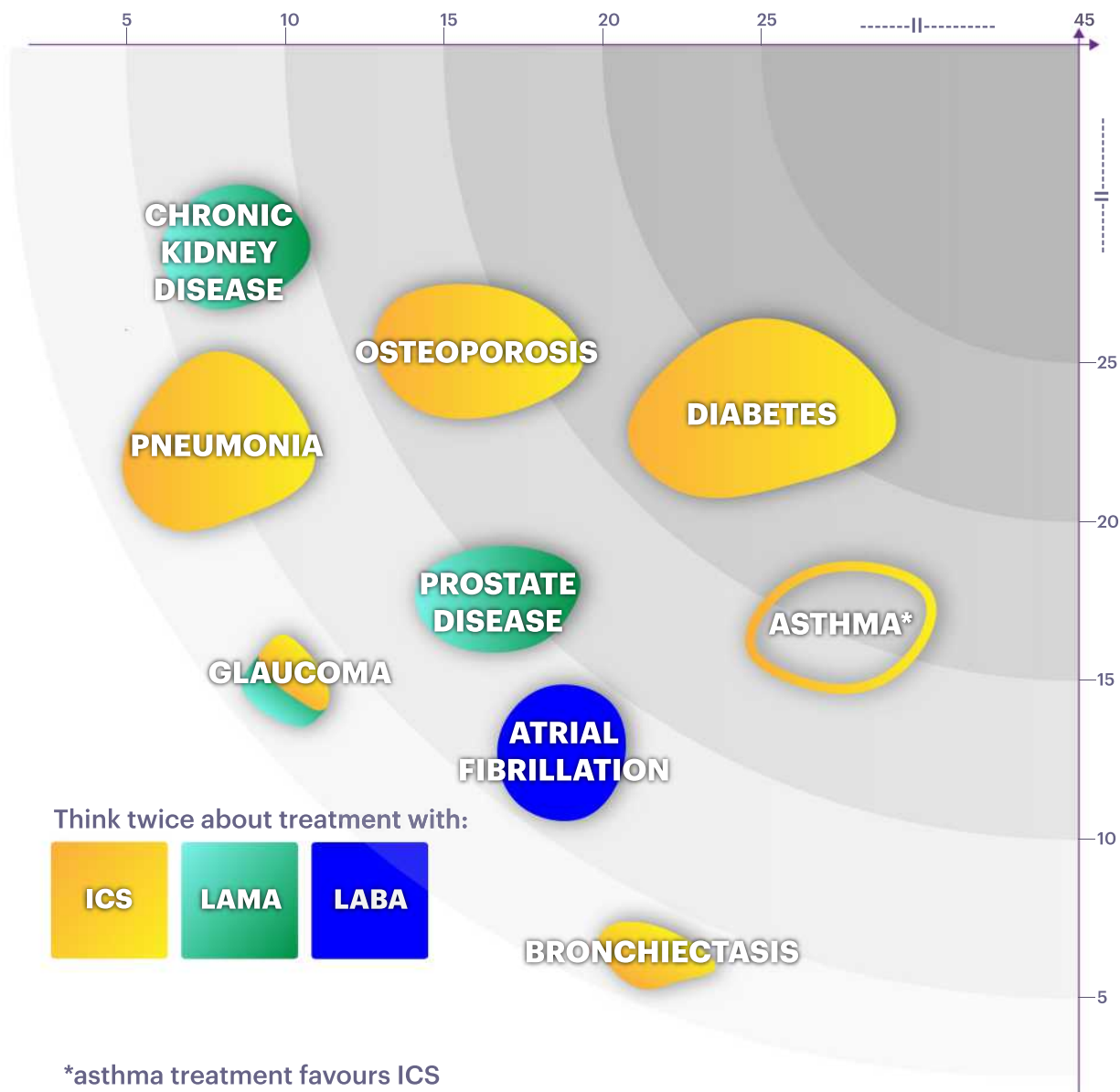


Figure 1(B) Visual interpretation of COPD medication recommendations[§]. [§]Pneumonia data based on Lipson²⁸ and Papi.²⁷

Abbreviations: COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroid (yellow); LABA, long-acting β_2 -agonist (blue); LAMA, long-acting antimuscarinic (green).

each year over a three-year period are rare (2%).³⁰ Since many studies have shown that the use of ICS increases the risk of pneumonia, the importance of the risk/benefit evaluation has been emphasized.^{28,37–39} Initial therapy with ICS in combination with a LABA may be the first choice only in selected patients, ie, patients with history of asthma, patients with a history of hospitalization(s) for exacerbations or ≥ 2 moderate exacerbations per year, despite appropriate long-acting bronchodilator treatment, and patients with blood eosinophil counts ≥ 300 cells/ μ L.¹³

Withdrawal of ICS must be considered if pneumonia, inappropriate original indication (eg, use of ICS to treat symptoms in the absence of a history of exacerbations) or lack of response to ICS occurs.¹³ Large studies have shown that gradual or abrupt withdrawal of ICS is feasible, and – according to Suissa’s analysis of the Quebec Health Insurance Database – may result in a reduction of severe pneumonia.^{40–43} Initiatives for withdrawal of inhaled corticosteroids in primary care are represented in Table 1.

Table 1 Initiatives for Withdrawal of Inhaled Corticosteroids in Primary Care

Initiator	Tool	Description
IPCRG	Desktop helper ⁷⁴	Easy tool developed by the IPCRG to help physicians identifying patients who would benefit from ICS treatment vs those in whom it may not be appropriate, and to provide guidance on how to withdraw ICS. Currently available in English, Spanish and Portuguese.
Sweden	Roadmap for ICS withdrawal	A quick reference document available in Swedish (http://www.naaka.se/images/pdf/Nedtrapping-ICS-vid-KOL-lathund.pdf)
Netherlands	ICS reduction tool ⁸⁶	Based on the Dutch GP guidelines and the IPCRG desktop helper, adapted for the Dutch situation; includes both identification of overuse and suggestions for monitoring after ICS deprescribing.
Belgium	ICS withdrawal questionnaire ⁸⁷	Five questions for daily practice developed by academic and non-academic chest physicians to provide guidance on (in) appropriate use of ICS and to train small focus groups of primary care physicians.

Abbreviations: IPCRG, International Primary Care Respiratory Group; ICS, inhaled corticosteroids.

The COPD treatment recommendations have substantially evolved over the past decades before arriving at their current stage. The uptake of changing recommendations into international and local guidelines and to primary care routine is usually slow, and the COPD case has encountered particularly high resistance.⁴⁴ Numerous examples illustrate the persistence of misalignment between guidance and current prescription patterns with over-prescription of LABA/ICS as a consequence.⁴⁵ The Greek UNLOCK study showed that more than 50% of patients were treated with a LABA/ICS independently of the GOLD classification. GPs mentioned many reasons for this non-adherence to guidelines such as lack of updates of the local guidelines, restricted access to diagnostic procedures, and local prescription-reimbursement rules.⁴⁴ A comparison of Swedish cohorts of COPD patients from both primary and secondary care found that maintenance treatment with LABA/ICS or ICS alone significantly decreased between 2005 and 2014, while a combination of

LABA/ICS plus LAMA had become the most commonly prescribed treatment in 2014.⁴⁶

Furthermore, non-adherence to available guidelines may be partially explained by a range of limitations of the ABCD grading system, that seem to be not very widely used among specialists and primary care physicians (eg, ERS, ATS, ALAT, SEPAR guidelines).^{47–49} Since 2019 the ABCD grading system applies only for the initial COPD treatment. Follow-up treatment suggestions are based on the treatable traits, dyspnea, and exacerbations.¹³

Inhaler Medication in the Multimorbid COPD Patient

Thanks to long-term and extensive use of inhaled medications in the past decades, well-established tolerability profiles are available for each of the three major treatment categories, ie, LAMA, LABA and ICS (Table 2). Bronchodilators appear to be generally safe. Known adverse reactions of LAMA are dry mouth (most frequent, 15% of patients), constipation, headache, pharyngitis, urinary retention and acute glaucoma (if used with face mask).^{12,13,50} With LABA, consideration is given to systemic effects, including tremor, tachycardia, palpitations and changes in plasma potassium concentrations.^{12,13} Historically, LAMA and LABA use in COPD patients with cardiovascular disease has always been in special focus of safety monitoring. Today, extensive evidence has accumulated to support the safety of these drugs.⁵¹ It seems that higher risk for cardiovascular events is associated with the comorbidities chronic cardiovascular and/or chronic kidney disease, and history of frequent exacerbations, rather than associated with the use of inhaled bronchodilators.⁵² Consequently, current debate starts to focus on how the patient's cardiovascular condition may benefit from appropriate COPD treatment.

ICS are generally safe but should be used with caution in patients with COPD who have no history of asthma, considering the risk/benefit ratio, particularly when patients have many comorbidities.¹³ Long-term use of ICS has been associated with many local and systemic side effects (pneumonia, tuberculosis, mycobacteria, bone fracture, ophthalmologic effects, diabetes, candidiasis and dental decline).^{53,54} Some ICS-containing medications include a warning on glaucoma and cataract with long-term use of ICS, and patients are advised to consult an ophthalmologist if ocular symptoms occur.^{53,54}

Managing multimorbid COPD patients is particularly challenging because of the large number of prescriptions and potential for adverse drug reactions.^{5,12} Patients with

Table 2 Most Important Adverse Events Related to Inhaled COPD Maintenance Treatment

Comorbid Category	Medication		
	ICS ^{13,54}	LAMA ¹³	LABA ^{13,88}
Cardiovascular			Tachycardia Rhythm disturbances (in susceptible patients)
Respiratory	Pneumonia Mycobacterial infection (including tuberculosis)		
Nervous system			Tremor
Urinary tract		Urinary symptoms	
Metabolic	Increased risk of diabetes Poor control of diabetes Decrease bone density/fractures		Hypokalemia (if combined with corticosteroids or thiazide diuretics)
Skin	Bruising		
Vision	Glaucoma Cataract	Glaucoma (if used with face mask)	
Oropharyngeal	Oral candidiasis Hoarse voice Dental decline	Dry mouth	

Abbreviations: COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroid; LABA, long-acting β_2 -agonist; LAMA, long-acting antimuscarinic.

COPD are often taking multiple (5 to 10) drugs simultaneously, while polypharmacy carries the risk that drugs with similar potential for adverse reactions are inadvertently combined.⁵⁵ A cross-sectional UK Biobank study found that the risk for adverse effects of treatment combinations is particularly high in patients with COPD. Medications contributing to this risk (falls, renal injury, constipation, urinary retention, depression, bleeding) were largely indicated for the management of other associated morbidities rather than COPD.⁵⁶ Still, these findings should be carefully discussed due to the low response rate of the participants (5% of the invited individuals participated in the study).

The situation becomes even more complex when comorbid conditions and adverse reactions to treatment look alike (Figure 1, panel B). The link between ICS use and reduced bone density, particularly in women with osteoporosis, the increased risk of diabetes, tuberculosis and pneumonia is a point of concern (Table 3).

Comorbidities of Special Interest

Asthma

While COPD and asthma are both inflammatory lung diseases, characterized by chronic airflow limitation, they are still two

distinct diseases, that overlap.¹³ However, patients with asthma may have a higher risk for developing COPD.⁵⁷ It is currently estimated that both diseases co-exist in 10 to 20% of COPD patients.^{13,57,58} These patients with asthma-COPD overlap (ACO) have clinical features of both asthma and COPD, more intense eosinophilic bronchial inflammation, more severe respiratory symptoms and more frequent exacerbations.⁵⁹ Recognizing the asthma component in COPD patients, which requires ICS prescription, is crucial.⁶⁰

Osteoporosis/Fractures

Osteoporosis is often underdiagnosed; women require particular consideration in this regard.⁶¹ Reduced bone density has been associated with ICS use, which increases the risk for fractures.^{62,63} In the meta-analysis of Loke et al, each 500 μg increase in beclomethasone dose equivalent was paralleled with 9% increased risk of fractures.⁶³ In the real life DACCORD cohort of 6611 COPD patients, exposure to ICS was associated with an increased risk of osteoporosis and should be taken into consideration.⁶⁴ Moreover, repeated courses of systemic corticosteroids significantly increase the risk of osteoporosis and should be avoided if possible.¹³

Table 3 Relationship Between COPD Comorbidities and ICS Treatment

Concomitant Condition	ICS Treatment	Ref
COPD	S If response to bronchodilator treatment is insufficient, adding ICS may be considered if blood eosinophil counts ≥ 300 cells/ μ L or ≥ 100 cells/ μ L in COPD patients with ≥ 2 moderate exacerbations* or ≥ 1 exacerbation requiring hospitalization. Initiation therapy with LABA/ICS may be the first choice in selected COPD patients (symptomatic with frequent exacerbations and blood eosinophil counts ≥ 300 cells/ μ L). A follow-up treatment in combination with LAMA and/or LABA, in selected patients	[13]
Asthma	R LABA/ICS may be first choice in COPD patients with a history of asthma and asthma-COPD overlap	[13]
Pneumonia	C Regular treatment with ICS increases the risk of pneumonia, particularly in patients with severe COPD. De-escalation of ICS must be considered.	[13]
Osteoporosis/fractures	C ICS have been associated with increased bone loss and fracture risk. Consideration in women.	[61–63]
Diabetes and pre-diabetes	C ICS, particularly high doses, have been associated with onset and progression of diabetes.	[65,66]
Bronchiectasis	C ICS may not be indicated in patients with bacterial colonization or recurrent lower respiratory tract infections.	[13,84]
Mycobacterial infection (including tuberculosis)	C ICS, particularly high doses, were shown to increase the risk of tuberculosis.	[71]

Notes: *Moderate exacerbation: defined as exacerbation treated with short-acting bronchodilators plus antibiotics and/or oral corticosteroids.¹³

R, Recommended (green); **S**, Selected patients (yellow); **C**, Caution (red).

Abbreviations: COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroid; LABA, long-acting β_2 -agonist; LAMA, long-acting antimuscarinic.

Diabetes

Diabetes occurs frequently in COPD but the prevalence varies across epidemiological studies.⁵ Administration of ICS has been reported to augment new onset of diabetes as well as progression.^{65,66} According to the historical matched cohort study of Price et al, prescribing ICS to COPD patients with type 2 diabetes had a negative impact on diabetes control: increase in HbA1C levels, more diabetes-related general practice visits, and more prescription of glucose strip compared with matched patients not prescribed ICS.⁶⁶ Higher cumulative doses of ICS were associated with higher risk of diabetes progression. Importantly, the authors pointed to the fact that some effects were stronger in mild-to-moderate COPD patients, who should not have received ICS according to the treatment guidelines. Similarly, the analysis of patients with respiratory disease of the Quebec health insurance database showed that current use of ICS was associated with 34% increase in onset of diabetes in patients initially free of diabetes and 34% increase in the rate of diabetes progression to use of insulin among users of oral hypoglycemic agents.⁶⁵ The risk increased with higher doses of ICS.

Based on the Australian retrospective study of administrative claims data, Caughey et al recommended constant revision of corticosteroid dose (inhaled and systemic) in patients with diabetes and COPD, to ensure that the lowest effective doses are used.⁶⁷ Admission to hospital for diabetes complications was 94% more likely in patients who received ≥ 0.83 DDD (total defined daily dose) than in those who were not treated with corticosteroid.

Pneumonia and Tuberculosis

The Swedish ARTIC study demonstrated that patients with COPD have a more than four-fold greater risk of pneumonia compared with the matched non-COPD reference group.⁶⁸ In patients with mild to moderate COPD ($FEV_1 \geq 50\%$) using ICS, the risk of pneumonia increased by 20–30% compared with patients not using ICS.⁶⁸ Aligned with this finding, GOLD 2021 and ERS 2020 recommend to withdraw ICS amongst other reasons (eg, patients without frequent exacerbations, history of frequent exacerbations and < 300 eosinophils cells/ μ L), also if adverse events, such as pneumonia occur.^{13,69} Moreover, the meta-analysis performed by Pavord et al reported that patients with a low baseline blood eosinophil count (< 150 – 200 cells/ μ L) are at increased risk of pneumonia.⁷⁰ This finding is

also reflected in the GOLD 2020 recommendations, considering a strong support for ICS if history of hospitalizations for exacerbations of COPD, ≥ 2 exacerbations per year (despite long acting bronchodilation), history of concomitant asthma, and a consideration of use if blood eosinophil counts 100–300 cells/ μL , one moderate exacerbation of COPD per year (despite long acting bronchodilation). Most importantly, GOLD suggests no use/withdrawal in repeated pneumonia events, blood eosinophils < 100 cells/ μL , history of mycobacterial infection.¹³

Suissa et al calculated, using the Quebec health insurance databases, that discontinuation of ICS was associated with a 37% decrease in the rate of serious pneumonia.⁴² The risk reduction was already evident in the first month (20% reduction) and further decreased to 50% by the fourth month of withdrawal.

Another analysis of the Quebec health insurance database found that the use of ICS was also associated with an increase of tuberculosis development.⁷¹ The association was dose-dependent.

Atrial Fibrillation

Atrial fibrillation may occur as a comorbidity in patients with worsening COPD.¹³ In the past, concerns have been raised about the potential arrhythmogenic risk of bronchodilators. In the meantime, this has been the object of research in clinical trials, including patients at risk, which showed that the risk was acceptable.^{13,72,73} According to GOLD 2021, available evidence suggests an overall acceptable safety profile for LABA, LAMA (and ICS). Nevertheless, caution is advised when using short-acting β_2 -agonists and theophylline, which may precipitate atrial fibrillation and make control of the ventricular response rate difficult.¹³ Still, further research, such as post-marketing surveillance or real-world studies, is required to sufficiently assess this topic and avoid challenges related to sample representativeness and external validity. The GOLD guidelines do not recommend altered treatment in the presence of atrial fibrillation,¹³ but caution may be advisable in susceptible patients.⁷⁴ Evidence also confirms that β_2 -agonists and selective β_1 -antagonists can be used concomitantly in the management of coexisting COPD and heart failure.¹³

Other Diseases and Interactions

Glaucoma has been reported when LAMA is used with face mask.¹³ The use of ICS has been associated with visual impairment (eg, cataract, glaucoma).⁷⁵

Urinary symptoms have been reported in patients taking LAMA, but the causal relationship has not been established.^{13,76} Men with lower urinary tract symptoms (LUTS) or benign prostatic hyperplasia (BPH) may develop acute urinary retention when treated with LAMA.⁷⁷ In patients with moderate to severe renal impairment, LAMA should only be used if the expected benefits outweigh the potential risk. Special attention is required with anticoagulant treatment in patients susceptible to easy bruising (adverse effect of ICS).⁵⁴ Also, concomitant use of common drugs that are CYP3A4 inhibitors (eg, ketoconazole, clarithromycin, verapamil and ingestion of grapefruit) may increase the bioavailability and risk of ICS.⁷⁸ The occasional use of systemic corticosteroids should also require consideration as it increases the steroid burden and may increase the risk of ICS-related adverse effects.⁵⁴

Phenotypes and Treatable Traits

In addition to focus on COPD patients' co-morbid conditions, other patient characteristics, so-called phenotypes may be relevant, especially in multimorbid COPD patients. There is increasing interest in phenotyping of COPD patients to guide clinical practice to the needs of the individual patient.⁷⁹

Common clinical phenotypes include patients with low exacerbation risk, frequent exacerbators with emphysema, frequent exacerbators with chronic bronchitis and patients with asthma-COPD overlap.⁸⁰ Bronchodilators are the preferred treatment option in non-frequent exacerbators, except for patients with asthma-COPD overlap, who should always be treated with ICS in addition to bronchodilators. In persistent exacerbators, the role of blood eosinophils as biomarker has gained importance, since there are alternatives to ICS, such as roflumilast in some countries (appropriate in patients with chronic bronchitis) and azithromycin (appropriate in selected patients with frequent infections and/or bronchiectasis and initiated by a pulmonologist).^{13,80} In the treatment algorithm for follow-up, GOLD 2021 differentiates patients according to the treatable trait, dyspnea or exacerbations.¹³

From this perspective, some interesting findings, to take into consideration, are listed below: (1) Eosinophilic airway inflammation can be considered a treatable trait identified via high eosinophil counts.⁷⁰ (2) Patients with emphysema may have a higher risk of lung cancer, osteoporosis and loss of muscle mass.^{72,81} (3) Cigarette smoking is a major risk for COPD and

cardiovascular disease, osteoporosis, and lung cancer.²¹ Reduced responsiveness to the anti-inflammatory effects of steroids, make ICS less helpful in smoking COPD patients.⁸² (4) Over 50% of COPD patients have an altered airway microbiome, and the frequency of exacerbations was found higher in patients with colonization of the lower airways.⁸³ Long-term ICS treatment affected the bacterial load, particularly in patients with low eosinophil counts.⁸⁴ (5) Older patients and patients with low body mass index are at increased risk for pneumonia and loss of muscle mass. (6) Physicians should also consider that bronchiectasis and interstitial lung diseases may occur in these patients.

How to Manage in Routine Clinical Practice

While the GOLD recommendations raise “reduce risk (prevent and treat exacerbations)” as a primary goal of COPD treatment, our panel suggested to expand this goal to “reducing the risk of exacerbations and the risk of adverse health events that may affect the patient in the future”.

The management of multimorbid COPD patients is - per definition - personalized medicine. Physicians should adopt systematic ways to follow COPD patients. Herein, multimorbidity should be taken as a call to action to reconsider COPD treatment. This is due to the fact that, multimorbid patients who comprise the vast majority of the COPD population are at greater risk of adverse outcomes and treatment complications, they are more likely to receive ineffective care or have lower adherence to treatment,⁸⁵ have higher health care costs, and worse survival. Therefore, this group of COPD patients requires a personalized treatment plan that takes into account individual ability to cope with day-to-day activities, adhere to medication, additional needs for healthcare services and multiple regular medicines, long-term physical and mental health conditions, frailty or falls and unplanned emergency hospitalizations.¹⁶

Also, the interface between symptoms of comorbid diseases and side effects of medication should be considered. Especially if comorbidities as diabetes, atrial fibrillation, osteoporosis/fractures, infections (pneumonia and tuberculosis) or asthma are present, it is important to carefully consider the individual risk/benefit balance when prescribing medication, ie, discontinuation of ICS treatment in patients without an appropriate indication for ICS,

while prescribing ICS-containing treatment in patients who need it according to the treatment guidelines. One should not forget simple preventative measures, such as vitamin D - calcium supplementation in case of osteoporosis risk.

Initiatives to integrate COPD into the holistic consultation may be an interesting incentive in primary care. Nurses and patient associations may also help in getting the messages to the patients, because patients often do not discuss their symptoms of COPD. Good coordination of first, and second-line patient management is required. The approach depends on the availability of local resources but should always properly consider patient benefits.

In summary, to improve the management of comorbid COPD patients, the following points should be considered:

Pay attention to co-morbid conditions; monitor and consider how COPD medications may potentially influence the comorbid diseases.

In the primary care setting, assess at least annually patient treatments and adjust medications as appropriate. This will allow re-adjustment of the individualized care plan, check inhalation technique and adherence to treatment, avoid unnecessary medication (especially ICS overuse or misuse in the context of comorbidity) and reveal new needs of the patient, enhance quality of life and minimize treatment burden and healthcare costs.

Integrate assessment of comorbidities and drug interactions in medical practice software to trigger alerts (eg, monitoring for diabetes if ICS is prescribed).

Empower multimorbid COPD patients to cope with disease- and medication-related information. Short advice and patient/caregiver counselling sessions about self-management may respond to their physical and mental needs and help to reduce anxiety and risk for depression.

Consider price and adherence to medication, including stopping of inappropriate medication.

Carefully evaluate the indication before initiating ICS treatment.

Conclusions

Since comorbidities are frequent in COPD patients, there is an urgent need for specific recommendations to guide physicians in their multimorbid approach. The current work reflects on the benefit/risk of current inhaled medications in a point-by-point and graphical way, in order to help physicians, who manage these multimorbid and poly-medicated patients in daily practice.

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Author Contributions

All authors made a significant contribution to the work reported, in the conception, study design, execution, acquisition of data, analysis and interpretation; they took part in drafting, revising and critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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IT received honoraria for talks and advisory boards of Novartis, GSK, Boehringer Ingelheim, grants from Elpen, GSK Greece, Astra Zeneca Greece, outside the submitted work.

KH has received honoraria for educational activities and lectures from AstraZeneca, Boehringer Ingelheim, GSK, Novartis, Novo Nordisk, and Sanofi, and has served on advisory boards arranged by AstraZeneca, Novartis, GSK, Sanofi, Boehringer Ingelheim, Teva and Chiesi.

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