Rational Use of Inhaled Medications for the Patient with COPD and Multiple Comorbid Conditions: Guidance for Primary Care

INTRODUCTION
Chronic obstructive pulmonary disease (COPD) is typically accompanied by multiple comorbid conditions. However, guidelines for the management of patients with COPD focus on the disease itself, providing little practical guidance on the routine management of comorbidities. Our objective is to review the impact of comorbidities on treatment choices for patients with COPD, especially with regard to the risks and benefits of inhaled medications including long-acting beta-agonists (LABA) and long-acting muscarinic antagonist (LAMA) and with a special focus on inhaled corticosteroids (ICS).

MULTIMORBIDITY IN COPD
Patients with COPD typically present with multiple comorbid conditions which require long-term management alongside their COPD. An additional challenge is that concomitant conditions, such as asthma or bronchiectasis, can be overlooked because signs and symptoms may overlap with those associated with COPD. Over 85% of adult patients with COPD will have at least one comorbid condition of clinical relevance, half of them have three or more. The prevalence of comorbidities increases with worsening COPD severity in both men and women and women appear to have a greater susceptibility to asthma, osteoporosis, anxiety and depression but appear less likely to have cardiovascular disease than men.

Comorbidities often appear in clusters which suggests common risk factors (smoking and inactivity are risk factors for both COPD and lung cancer), shared underlying pathological mechanisms (accelerated ageing is associated with both COPD and hypertension) and side effects of COPD treatment (development of diabetes).

MANAGING THE PATIENT WITH COPD
According to the latest recommendations of the Global Initiative for Chronic Obstructive Lung Disease (GOLD), bronchodilation remains the mainstay of treatment for patients with stable COPD. Patients should be initiated on single or dual long-acting bronchodilator therapy. ICS/LABA can be considered as an initial therapy for patients in GOLD D with blood eosinophil counts ≥300 cells/µl. However, as ICS treatment may be associated with an increased risk of pneumonia, a risk-benefit evaluation is warranted for individual patients and withdrawal of ICS must be considered in case of emergent pneumonia.

MANAGING THE MULTIMORBID PATIENT WITH COPD
The management of individual patients with COPD and multimorbidity is often complex requiring the simultaneous application of several disease-specific treatment guidelines. These guidelines are rarely aligned with regard to treatment recommendations; therefore a holist approach is of particular importance for patients with multimorbidity. We would encourage primary care physicians to undertake regular (at least annual) (re)assessment and treatment adjustment for patients with COPD. Emergence of multimorbidity should be regarded as a signal and call to action to undertake a review of COPD treatment with a focus on the interface between symptoms of their comorbid diseases, treatment adherence and side effects of medication.

For patients with COPD, multimorbidity is associated with a high level of polypharmacy and an increased risk for adverse drug reactions and interactions as well as an increased risk of hospitalisation and premature death. Polypharmacy is of particular concern when drugs with potential for similar adverse reactions are combined.

In general, multimorbidity should not delay or alter the treatment of COPD and comorbidities should be managed according to usual standards; attention should be directed to ensure treatment simplicity and to minimise polypharmacy.

COMORBIDITIES OF SPECIAL INTEREST
The management of patients with COPD and multimorbid conditions requires a personalised approach. Primary care physicians should adopt systematic ways to monitor patients with COPD. The interface between symptoms of comorbid diseases and side effects of medication should also be considered with special attention paid to the following comorbidities:

- Asthma
- Osteoporosis/fractures
- Diabetes
- Pneumonia and tuberculosis
- Atrial fibrillation
- Chronic pain
- Chronic kidney disease
- Prostate disease
- Gastroesophageal reflux
- Anxiety and/or depression
- Obstructive sleep apnoea
12. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Chronic Obstructive Lung Disease 2020 Global Strategy for Prevention, Diagnosis and Management of COPD. Available at: https://goldcopd.org/goldreport/.

### Treatment considerations for the multimorbid patient with COPD

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>COPD treatment-associated risks</th>
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<tbody>
<tr>
<td>Asthma</td>
<td>Recommended, LABA/ICS may be first line in patients with COPD and a history of asthma and asthma-COPD overlap. Recommended in selected patients.</td>
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<tr>
<td>Pneumonia</td>
<td>Increased risk of pneumonia; consider withdrawal of ICS and maximize bronchodilator.</td>
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<tr>
<td>Osteoporosis/ fractures</td>
<td>Increased bone loss and fracture risk; of particular concern in women.</td>
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<tr>
<td>Diabetes and pre-diabetes</td>
<td>Associated with onset and progression of diabetes, especially at higher doses.</td>
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<td>Bronchiectasis</td>
<td>Not indicated in patients with bacterial colonization or recurrent lower RTI.</td>
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<tr>
<td>Tuberculosis</td>
<td>Increased risk for TB, particularly at high doses.</td>
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<tr>
<td>Chronic kidney disease</td>
<td>Associated with urinary symptoms.</td>
</tr>
<tr>
<td>Prostate disease</td>
<td>Associated with urinary symptoms.</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>Associated with tachycardia and rhythm disturbances (in susceptible patients).</td>
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<tr>
<td>Glaucoma</td>
<td>Associated with glaucoma and cataracts.</td>
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</table>

**COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroid; LABA, long-acting beta-agonist; LAMA, long-acting muscarinic antagonist; RTI, respiratory tract infection, TB, tuberculosis.**

- **Recommended**
- **Use with caution**
- **Use as per COPD guidelines**