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Tailoring treatment of patients with COPD

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Patients with COPD are treated with drugs to improve the breathing ability in combination with inhaled corticosteroids to reduce the risk of acute worsening of the lung conditions. But the balance between reduced exacerbations and increased adverse effects of the drugs depends on the dose and on patient characteristics. Researchers from the University of

Zurich now show how to personalize treatments to optimally balance benefits and side effects.

Patients with chronic obstructive pulmonary disease (COPD) suffer from a permanent narrowing of the airways making breathing difficult. The narrowing is caused by inflammation of the small airways, resulting in mucus production and destruction of lung tissue. Inhaled corticosteroids are commonly used in combination with long-acting bronchodilators to prevent acute worsening of the lung condition—so-called exacerbations—in patients with COPD. While inhaled corticosteroids reduce inflammation or exacerbations, bronchodilators improve breathing by broadening the bronchi.

Benefit of inhaled corticosteroids depends on three factors

There is a longstanding debate about the use of inhaled corticosteroids in the heterogeneous and wide range of COPD patients. Guidelines propose a personalized treatment approach, but they remain rather vague, since it is unclear for whom the benefits outweigh the harmful side effects. A study lead by Henock Yebyo, postdoctoral researcher at the Epidemiology, Biostatistics and Prevention Institute of the University of Zurich (UZH), now sheds light on this challenge. "Our results show that three key factors influence the balance of treatment benefits and side effects of adding different doses of inhaled corticosteroid: The risk of exacerbation, the amount of certain blood cells and the patient's age," says first author Yebyo.

Systematic consideration of treatment and patient characteristics

The researchers considered many characteristics of treatments and

patients that have an influence on the balance of reducing exacerbations and increasing side effects. Comprehensive statistical analyses were performed to calculate how high the risk for exacerbations must be for the benefit of reducing these exacerbations to outweigh the side effects, which includes severe pneumonia, oral thrush, and a hoarse voice. They found that patients with a two-year exacerbations risk of less than 32%—typically those who did not have exacerbations in the past—do not benefit from low to moderate dose inhaled corticosteroids.

While the guidelines did not consider the dose of the inhaled corticosteroids, this study clearly shows that high doses are associated with considerable side effects which may outweigh the benefits. Patients above the age of 80 are unlikely to benefit, because they are at increased risk for pneumonia which outweighs the reduction in exacerbations. On the other hand, patients with certain blood cells typical for asthma—the so-called eosinophils—are more likely to benefit.

Systematic approach facilitates tailored COPD treatment

When applying these results to data from a Swiss and Dutch COPD cohort study, the researchers showed that some patients are overtreated with inhaled corticosteroids while others are undertreated. "Our results may not necessarily lead to less use of inhaled corticosteroids, but helps to minimize over- and underuse by tailoring treatment according to dose and patient characteristics," says Henock Yebyo.

Precision medicine is often broken down to single factors like a genetic marker, but the reality is usually more complicated. Using a systematic approach, the UZH researchers considered three categories of factors influencing the outcome and combined them comprehensively: factors that modify treatment effects, factors associated with the likelihood of

benefits and side effects without treatment and patient preferences. "Our study may serve as an example of how the complexity of the benefit-harm balance can be approached in a systematic way so that treatment guidelines can provide specific and useful recommendations on how to personalize treatments," says UZH professor Milo Puhan.

More information: Henock G Yebyo et al, Personalising add-on treatment with inhaled corticosteroids in patients with chronic obstructive pulmonary disease: a benefit–harm modelling study, *The Lancet Digital Health* (2021). DOI: 10.1016/S2589-7500(21)00130-8

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