Therapeutics Initiative
Better prescribing. Better health.

THERAPEUTICS LETTER 145
October 2023

Minimizing inhaled corticosteroids for COPD

Plain Language Summary

What is Chronic Obstructive Pulmonary Disease (COPD)?

COPD can become a serious lung condition that makes it hard to breathe. Airways in the lungs get inflamed and narrow, making it difficult for air to flow in and out.

What causes COPD?

The main cause is smoking cigarettes. Breathing in air pollution or chemical fumes can also be harmful.

How can we help people with COPD?

There are medicines that can help with COPD. They don't help over time if people continue to smoke. The medicines can help improve symptoms so that people can be more active and healthier.

What about inhaled corticosteroids (ICS)?

Because inhalers improved breathing in asthma, doctors thought ICS might be helpful for COPD. Studies later showed that ICS did not improve either symptoms or quality of life. They did not increase the chances of living longer. ICS can also have serious side effects including pneumonia and bone-thinning leading to fracture risk. Although ICS may improve asthma symptoms, COPD is a different illness and they don't help.

Who should use ICS?

Now, doctors are asked to only prescribe ICS in the most severe cases of COPD. In most cases, different medicines are used that widen the airways and help you breathe (bronchodilators).

Are there risks with using ICS?

Yes. Even short-term use of ICS can lead to an increased risk of both pneumonia and fractures from bone-thinning.

What should doctors do?

For milder COPD cases, patients should start and be limited to bronchodilators. For advanced cases, with severe shortness of breath, or if there are have been infections and hospitalizations, then ICS could be added. For people with milder disease who have been prescribed ICS in the past, doctors should try to gradually stop ICS.

Conclusions:

For most people with COPD, studies show that the harms from using ICS outweigh the benefits.

Abstract

Background: Therapeutics Letter 145 considers the evidence for inhaled corticosteroids (ICS) as a treatment for Chronic Obstructive Pulmonary Disease (COPD). This condition is characterized by airway inflammation and irreversible airflow obstruction that causes significant respiratory symptoms and reduced quality of life. Cigarette smoking is the main cause. Stopping smoking helps symptoms and slows disease progression and improves symptoms. Drug therapy aims to alleviate symptoms, enhance functional capacity and prevent exacerbations, but has not shown by randomized trials to reduce mortality or improve quality of life.

Findings: ICS have shown limited benefits for COPD symptoms and exacerbations but increased risks of serious harms. Guidelines recommend limiting ICS to severe COPD and only for repeated exacerbations. Studies show withdrawing ICS can be done safely for stable COPD patients with infrequent exacerbations, especially those with lower eosinophil counts. Provincial, national, and international guidelines now recommend limiting ICS prescriptions to severe COPD stages. Long-term ICS use may lead to serious side effects, including pneumonia and fractures.

Conclusions: Initial COPD therapy should focus on short-acting bronchodilators, not ICS. Adding long-acting bronchodilators is recommended before considering ICS due to limited benefits and risks of serious harms. For persistent symptoms, long-acting muscarinic agonists or long-acting beta agonists are recommended, with the addition of ICS reserved for those with repeated exacerbations. Deprescribing ICS can be considered in clinically stable patients, particularly for those with infrequent exacerbations. When applicable, tapering ICS over several months is advised for patients with elevated eosinophil counts. Overall, the risks of serious harms from ICS typically outweigh their limited benefits for COPD patients

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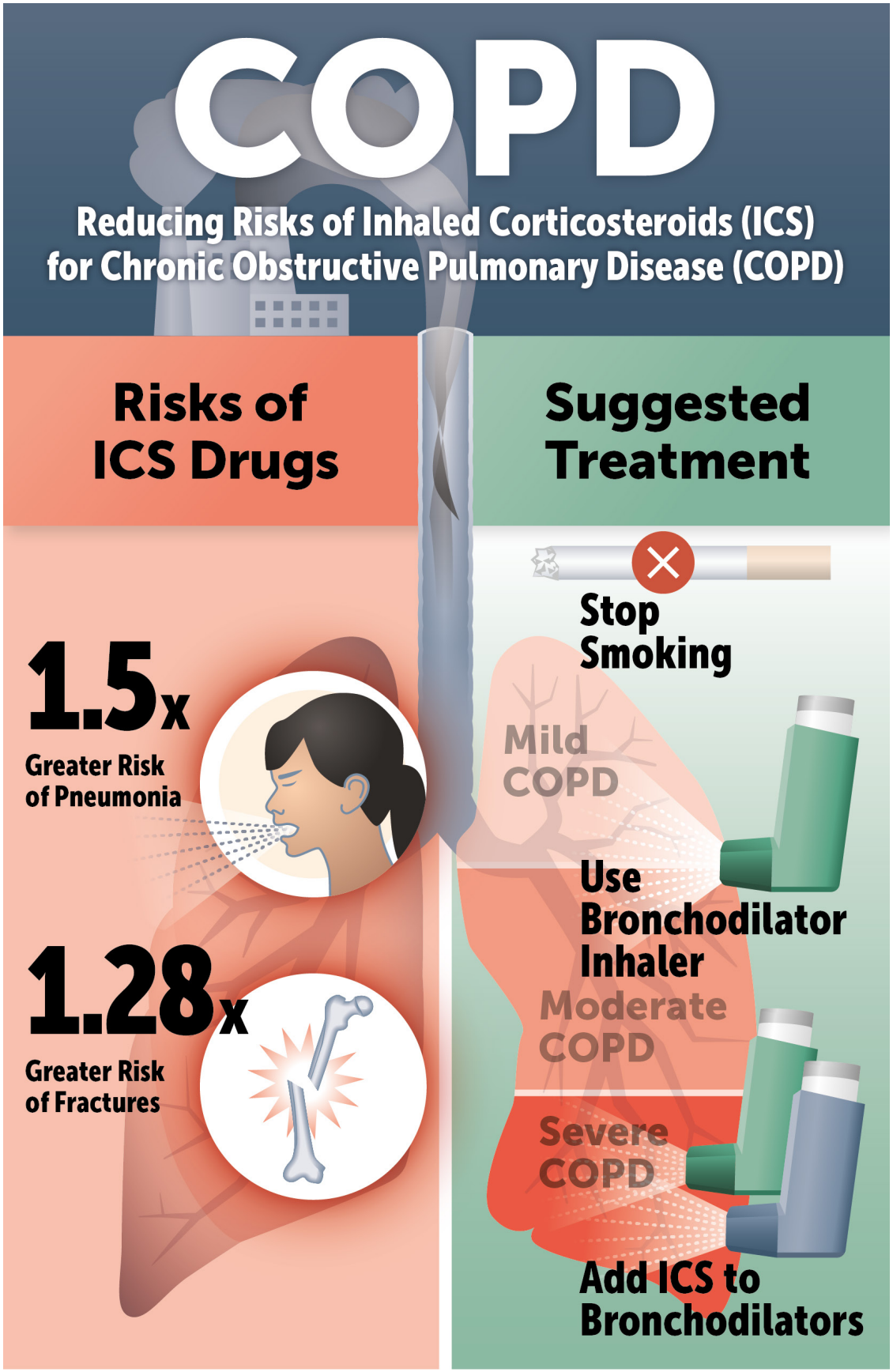

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Chronic Obstructive Pulmonary Disease (COPD) is characterized by airway inflammation and irreversible airflow obstruction that cause shortness of breath, cough, and excess mucus production, reducing quality of life. Permanent anatomical changes make bronchodilators less effective for COPD than for asthma.

Cigarette smoking is the principal cause, although long-term exposure to other lung irritants (including air pollution) also contributes. Stopping smoking improves symptoms, and is the only effective strategy to slow disease progression and reduce premature mortality.[1]

Acute exacerbations of COPD and bronchitis, typically due to infection, ranked second only to childbirth as a cause of hospitalization in Canada in 2018-2019, exceeding heart failure and myocardial infarction.[2] By 2020-2021, they ranked eighth (after COVID-19), but still over 47,000 admissions/year. In British Columbia their ranking declines, overshadowed by substance use disorders and major mental illness.[3]

Clinical goals of drug therapy are to reduce symptoms, improve functional capacity, and prevent exacerbations. Drug therapy has not been shown to reduce mortality.[4]

Inhaled corticosteroids: the evidence

Recognizing their efficacy for asthma, doctors began to prescribe inhaled corticosteroids (ICS) for COPD in the 1980's, without evidence from randomized controlled trials (RCTs).[5] Two decades later, RCTs had shown no mortality benefit from ICS compared with placebo, no reduction in the proportion of people experiencing an exacerbation, and no improvement in quality of life.[6-8] A possible explanation is that while corticosteroids potently suppress eosinophilic airway inflammation in asthma, the neutrophilic inflammatory process in COPD is typically steroid resistant.[5]

Provincial, national and international guidelines all recommend limiting prescription of ICS to the most severe stages of COPD.[9-11] During 2017-21, 51,128 British Columbians initiated drug therapy for COPD, of whom 27% received an ICS alone or in combination. This proportion was stable over the 5 years.[12] It is lower than in a large United Kingdom sample, in which 47% of COPD patients still received ICS as a component of initial daily drug therapy during 2015 (down from 77% in 2005).[13]

Serious harms from chronic inhaled corticosteroid use include pneumonia and fractures,[14] updated here from an unpublished 2020 TI meta-analysis.[15]

COPD guidelines discourage routine ICS prescription

Rational drug therapy employs the simplest and least expensive treatment to achieve individual therapeutic goals. For **initial therapy**, BC (2020) and Global initiative for chronic Obstructive Lung Disease (GOLD, 2022) guidelines recommend short-acting beta agonists (SABA) or short-acting muscarinic antagonists (SAMA) to relieve shortness of breath.[9,11]

For **worsening symptoms or to reduce exacerbations**, both recommend short and then long-acting bronchodilators (beta agonists/LABA or muscarinic antagonists/LAMA), alone or in combination.

Outcome (harm)	RCTs reporting outcome	Findings of TI meta-analysis (NNH: weighted mean duration of ICS)
Pneumonia requiring hospitalization	49 RCTs (n = 57,027) Fluticasone: 32 RCTs (n = 46,877) Budesonide: 17 RCTs (n = 10,150)	Fluticasone vs. non-ICS: • RR 1.50 (95% CI 1.34 to 1.68)* • ARI 1.1%; NNH 93 (21 months) Budesonide vs. placebo: • RR 1.60 (95% CI 1.01 to 2.55)* • ARI 0.5%; NNH 188 (9 months)
Total fractures	20 RCTs (n = 25,936) Fluticasone: 18 RCTs (n = 23,079) Budesonide: 2 RCTs (n = 2,857)	Fluticasone/budesonide vs. non-ICS: • RR 1.28 (95% CI 1.07 to 1.54) • ARI 0.42%; NNH 240 (16 months)

RR: relative risk; ARI: absolute risk increase; NNH: number needed to harm; * independent of ICS dose, duration, or baseline severity of COPD

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To LAMA + LABA, add ICS at the lowest possible dose **only for people who continue to experience repeated exacerbations**. GOLD and a 2020 Cochrane systematic review point out that no "escalation" strategy has been tested in RCTs,[11,16] while deprescribing ICS has been tested.

Can ICS be deprescribed safely?

Two recent manufacturer-funded studies evaluated ICS withdrawal, focusing on acute exacerbations, the most relevant clinical issue. Amongst 2,488 people with severe - very severe COPD who were susceptible to exacerbations, WISDOM (2014) **compared triple therapy** for up to 1 year (tiotropium 18 mcg/d + salmeterol 50 mcg twice/d + fluticasone 500 mcg twice/d) **with gradual withdrawal of fluticasone** over a 12-week period (followed by LAMA/LABA alone).[17] **Moderate or severe exacerbations were similar among people who discontinued or continued ICS therapy** (hazard ratio, 1.06; 95% CI 0.94 to 1.19). There were no clinically important between-group differences in symptoms, quality of life or safety. No patient subgroup had increased likelihood of exacerbations after stopping ICS.

Amongst 1,053 people **without frequent exacerbations**, SUNSET (2018) compared **continued triple therapy** for up to 26 weeks (tiotropium 18 mcg/d + salmeterol 50 mcg / fluticasone 500 mcg twice/d) **with abrupt discontinuation of ICS after long-term triple therapy**, replaced by once daily LAMA/LABA (indacaterol 110 mcg / glycopyrronium 50 mcg).[18] Annualized **moderate or severe exacerbations did not differ** between treatments (rate ratio 1.08; 95% CI 0.83 to 1.40). There was no difference in the time to first moderate or severe COPD exacerbation (hazard ratio 1.11; 95% CI 0.85 to 1.46).

SUNSET is the only RCT to report a pre-specified analysis of patient subgroups defined by baseline blood eosinophil counts, one approach to differentiating COPD (<300 cells/µL) from asthma (≥300 cells/µL). When baseline eosinophil count was <300/µL (COPD), stopping ICS made no difference to the rate of moderate or severe exacerbations, nor the time to exacerbation. In contrast, **in people with baseline eosinophils ≥300/µL (asthma/COPD overlap)**, stepdown to LAMA/LABA alone increased moderate or severe exacerbations vs. continuing ICS over 6 months (rate ratio 1.86; 95% CI 1.06 to 3.29).

Conclusions

- **Short-acting bronchodilators (SABA or SAMA), but not ICS, remain initial drug therapy for COPD.**
- **For persistent symptoms or exacerbations, adding LAMA or LABA, then LAMA + LABA, is recommended (but this strategy has not been tested in RCTs).**
- **For most people with COPD, the increased risk of serious harms from ICS outweighs the limited known benefits for symptoms or exacerbations.**
- **It is reasonable to try stopping ICS in clinically stable patients with infrequent exacerbations. For patients with eosinophils above 300/µL in a complete blood count, first taper ICS over a few months.**

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