

# Tripling out on COPD:

## The texture of COPD trials

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**disclosures**

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**SABA: short acting beta agonist**  
salbutamol (Ventolin MDI, Airomir MDI, generics, Ventolin Diskus)  
terbutaline (Bricanyl Turbuhaler)

**SAMA: short acting muscarinic antagonist**  
ipratropium (Atrovent MDI)

**SAMA+SABA**  
ipratropium + salbutamol (Combivent Respimat)

**LABA: long acting beta agonist**  
formoterol (Foradil Aerolizer)  
indacaterol (Onbrez Breezhaler)  
salmeterol (Serevent Diskus, Serevent Diskhaler)

**LAMA: long acting muscarinic antagonist**  
acclidinium (Tudorza Genuair)  
glycopyrronium (Seebri Breezhaler)  
tiotropium (Spiriva HandiHaler, Spiriva Respimat)  
umeclidinium (Incruse Ellipta)

**LAMA+LABA**  
acclidinium + formoterol (Duaklir Genuair)  
glycopyrronium + indacaterol (Ultibro Breezhaler)  
tiotropium + olodaterol (Inspiroto Respimat)  
umeclidinium + vilanterol (Anoro Ellipta)

**ICS+LABA: inhaled corticosteroid + long acting beta agonist**  
budesonide + formoterol (Symbicort Turbuhaler)  
fluticasone propionate + salmeterol (Advair Diskus, Advair MDI)  
fluticasone furoate + vilanterol (Breo Ellipta)

**ICS+LABA+LAMA**  
fluticasone furoate + vilanterol + umeclidinium (Trelegy Ellipta)

### Global Initiative for Chronic Obstructive Lung Disease GOLD 2018 guidelines

**for symptoms**

any bronchodilator

↓

LAMA or LABA

↓

LAMA+LABA

<https://goldcopd.org/>

2014 Cochrane Systematic Review  
**Tiotropium versus placebo**  
Health Related Quality of Life (SGRQ scale 0 to 100)  
2.89 point improvement

SGRQ improvement  $\geq$  4 points  
1 in 10 people ●●●●●●●●●●

2015 Cochrane Systematic Review  
**Tiotropium plus LABA (2 inhalers) vs tiotropium**  
Health Related Quality of Life (SGRQ scale 0 to 100)  
1.34 point improvement

SGRQ improvement  $\geq$  4 points  
1 in 14 people ●●●●●●●●●●●●●●

KARNER COCHRANE 2014 CD009285  
FARNE COCHRANE 2015 CD008989

### Global Initiative for Chronic Obstructive Lung Disease GOLD 2016 guidelines

Have you noticed a difference since starting this treatment?

Are you less breathless?  
Can you do more?  
Can you sleep better?

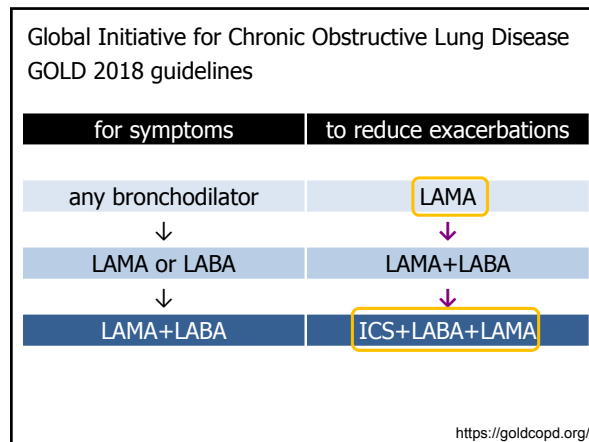
Is that change worthwhile to you?

<https://goldcopd.org/>



glycopyrronium + indacaterol	glycopyrronium	tiotropium
serious adverse events (ie, hospitalizations, disability, death)		
23%	24%	22%
COPD worsening (most frequent serious adverse event)		
15%	16%	12%

WEDZICHA Lancet Respir Med 2013;1:199-209



2016 Cochrane Systematic Reviews  
 tiotropium plus ICS/LABA vs tiotropium alone  
 (as 2 separate inhalers)

The current evidence is **insufficient** to support the benefit of tiotropium + LABA/ICS-based therapy for mortality, hospital admission or exacerbations

ROJAS REYES COCHRANE 2016 CD008532

IMPACT 2018 (triple vs. double combination therapy)  
 10,355 participants; trial duration: 52 weeks  
 symptomatic and ≥ 1 exacerbation in previous year  
 1 = 45%; 2 = 43%; ≥ 3 = 11%  
 mean age 65; 34% women; 78% White  
 35% current smokers; 65% former smokers

ICS+LABA+LAMA	ICS+LABA	LAMA+LABA
fluticasone + vilanterol + umeclidinium	fluticasone + vilanterol	umeclidinium + vilanterol

70% participants taking ICS prior to randomization (38% triple therapy)  
 subjects with a history of asthma were eligible if they have a current diagnosis of COPD  
 participants randomized to LAMA+LABA abruptly withdrawn from ICS at time of randomization

IMPACT NEJM 2018;378:1671-1680

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ICS+LABA+LAMA	ICS+LABA	LAMA+LABA
fluticasone + vilanterol + umeclidinium	fluticasone + vilanterol	umeclidinium + vilanterol
moderate – severe exacerbations (annual rate)		
0.91	1.07	1.21
triple vs ICS+LABA ↓ 0.16 exacerbation per year rate ratio 0.85 (95%CI 0.80 to 0.90)		triple versus LAMA+LABA ↓ 0.30 exacerbation per year rate ratio 0.75 (95%CI 0.70 to 0.81)
severe exacerbations (annual rate)		
0.13	0.15	0.19

IMPACT NEJM 2018;378:1671-1680

IMPACT 2018

main publication: "efficacy and safety analyses were performed in the intention-to-treat population"

appendix: "primary analysis of on-treatment moderate/severe COPD exacerbations"

10,355 randomized
7991 (77%) completed trial "on-treatment"

IMPACT NEJM 2018;378:1671-1680

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ICS+LABA+LAMA	ICS+LABA	LAMA+LABA
fluticasone + vilanterol + umeclidinium	fluticasone + vilanterol	umeclidinium + vilanterol
SGRQ at baseline: 51 (score 0 to 100)		
45.0	46.8	46.8
triple vs ICS+LABA 1.8 point difference out of 100		triple therapy vs LAMA+LABA 1.8 point difference out of 100
SGRQ improvement ≥ 4 points out of 100		
42%	34%	34%
missing data: 20%	missing data: 27%	missing data: 29%

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 35% current smokers; 65% former smokers

ICS+LABA+LAMA	ICS+LABA	LAMA+LABA
fluticasone + vilanterol + umeclidinium	fluticasone + vilanterol	umeclidinium + vilanterol
numbers of people diagnosed with pneumonia		
8%	7%	5%
triple versus LAMA+LABA HR 1.53 (95%CI 1.22 to 1.92)		
excluded people with risk factors for pneumonia eg, recent pneumonia or COPD exacerbation or RTI; immune suppression, Parkinson's Disease, very low BMI, severely malnourished, very low FEV1		

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 35% current smokers; 65% former smokers

ICS+LABA+LAMA	ICS+LABA	LAMA+LABA
fluticasone + vilanterol + umeclidinium	fluticasone + vilanterol	umeclidinium + vilanterol
people with serious adverse events (including COPD, pneumonia)		
22%	21%	23%

IMPACT NEJM 2018;378:1671-1680

Global Initiative for Chronic Obstructive Lung Disease  
 GOLD 2016 guidelines

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Is that change worthwhile to you?

<https://goldcopd.org/>

Global Initiative for Chronic Obstructive Lung Disease  
 GOLD 2018 guidelines

There is high quality evidence that ICS use is associated with oral candidiasis, hoarse voice, skin bruising and pneumonia

Patients at higher risk of pneumonia include:  
 current smokers, age ≥ 55, history of exacerbations or pneumonia, BMI < 25, poor dyspnea grade and/or severe airflow limitation

<https://goldcopd.org/>

ICS+LABA (wholesaler cost with markup up or fee)		
budesonide + formoterol (Symbicort Turbuhaler)	100 mg/6 mcg 200 mcg/6 mcg	\$70 asthma \$95 COPD, asthma
fluticasone propionate + salmeterol (Advair Diskus)	250 mcg/50 mcg	\$110 COPD, asthma
	500 mcg/50 mcg	\$155 COPD, asthma
fluticasone furoate + vilanterol (Breo Ellipta)	100 mcg/25 mcg	\$90 COPD, asthma
	200 mcg/25 mcg	\$140 asthma

**Pr BREO<sup>®</sup> ELLIPTA<sup>®</sup>**  
 BREO<sup>®</sup> ELLIPTA<sup>®</sup> 100/25 mcg once daily is the only strength indicated for the treatment of COPD. BREO<sup>®</sup> ELLIPTA<sup>®</sup> 200/25 mcg is not indicated for patients with COPD. There is no additional benefit of the 200/25 mcg dose compared to the 100/25 mcg dose and there is a potential increased risk of pneumonia and systemic corticosteroid-related adverse reactions.




<https://health-products.canada.ca/dpd-bdpp/index-eng.jsp>

## Safe Use of Newer Inhalation Devices

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### Breezhaler (dry powder inhalers)





*Usual Dose: Contents of 1 capsule inhaled daily\*\**

<p><b>Onbrex Breezhaler</b> indacaterol 75 mcg per capsule</p> 	<p><b>Safety Considerations and Counselling Tip:</b></p> <ul style="list-style-type: none"> <li>• Capsules are for inhalation only; they must not be swallowed.** Capsules can mistakenly be placed into the inhaler mouthpiece, resulting in treatment ineffectiveness and/or expiration of the entire capsule.</li> <li>• If swallowed by accident, skip the dose.</li> <li>• Capsules are packaged separately from the inhaler and must be inserted into the capsule chamber.** The mouthpiece must be opened to prevent capsule placement inside the capsule chamber.</li> <li>• If the chamber is not immediately emptied after use, pieces of the capsule can remain inside and impede the flow of product for the next dose.</li> <li>• Closed the capsule directly into the garbage without touching. Wash hands.</li> </ul>
<p><b>Saxbe Breezhaler</b> glycopyrronium 50 mcg per capsule</p> 	<p><b>Safety Considerations and Counselling Tip:</b></p> <ul style="list-style-type: none"> <li>• Capsules are for inhalation only; they must not be swallowed.** Capsules can mistakenly be placed into the inhaler mouthpiece, resulting in treatment ineffectiveness and/or expiration of the entire capsule.</li> <li>• If swallowed by accident, skip the dose.</li> <li>• Capsules are packaged separately from the inhaler and must be inserted into the capsule chamber.** The mouthpiece must be opened to prevent capsule placement inside the capsule chamber.</li> <li>• If the chamber is not immediately emptied after use, pieces of the capsule can remain inside and impede the flow of product for the next dose.</li> <li>• Closed the capsule directly into the garbage without touching. Wash hands.</li> </ul>
<p><b>Vibrona Breezhaler</b> indacaterol 110 mcg / glycopyrronium 50 mcg per capsule</p> 	<p><b>Safety Considerations and Counselling Tip:</b></p> <ul style="list-style-type: none"> <li>• Capsules are for inhalation only; they must not be swallowed.** Capsules can mistakenly be placed into the inhaler mouthpiece, resulting in treatment ineffectiveness and/or expiration of the entire capsule.</li> <li>• If swallowed by accident, skip the dose.</li> <li>• Capsules are packaged separately from the inhaler and must be inserted into the capsule chamber.** The mouthpiece must be opened to prevent capsule placement inside the capsule chamber.</li> <li>• If the chamber is not immediately emptied after use, pieces of the capsule can remain inside and impede the flow of product for the next dose.</li> <li>• Closed the capsule directly into the garbage without touching. Wash hands.</li> </ul>

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### Ellipta (dry powder inhalers)

*Usual Dose: 1 inhalation daily\*\**

<p><b>Anoro Ellipta</b> fluticasone 4.2 mcg / vilanterol 25 mcg per actuation</p> 	<p><b>Arcadya Ellipta</b> fluticasone 100 or 200 mcg per actuation</p> 	<p><b>Safety Considerations and Counselling Tip:</b></p> <ul style="list-style-type: none"> <li>• The foil packaging and desiccant must be discarded immediately after opening.**</li> <li>• The coloured cap should be opened before inhaling the dose. There is an audible "click" when the dose is ready to be inhaled.**</li> <li>• If the device cover is opened and then closed without inhalation of the loaded dose, that dose will be lost.** If a dose is lost, another dose can be loaded by opening the device cover again; double dosing will not occur.</li> <li>• If the device is tipped past horizontal, medication can fall out of the mouthpiece.</li> <li>• When there are less than 10 doses remaining, the left half of the counter shows red.</li> </ul>
<p><b>Breo Ellipta</b> fluticasone 100 or 200 mcg / vilanterol 25 mcg per actuation</p> 	<p><b>Incruse Ellipta</b> fluticasone 42.3 mcg per actuation</p> 	<p><b>Safety Considerations and Counselling Tip:</b></p> <ul style="list-style-type: none"> <li>• The foil packaging and desiccant must be discarded immediately after opening.**</li> <li>• The coloured cap should be opened before inhaling the dose. There is an audible "click" when the dose is ready to be inhaled.**</li> <li>• If the device cover is opened and then closed without inhalation of the loaded dose, that dose will be lost.** If a dose is lost, another dose can be loaded by opening the device cover again; double dosing will not occur.</li> <li>• If the device is tipped past horizontal, medication can fall out of the mouthpiece.</li> <li>• When there are less than 10 doses remaining, the left half of the counter shows red.</li> </ul>



[https://www.ismp-canada.org/download/safetyBulletins/2016/ISMPCSB2016-03\\_InhalationDevices.pdf](https://www.ismp-canada.org/download/safetyBulletins/2016/ISMPCSB2016-03_InhalationDevices.pdf)

## Safe Use of Newer Inhalation Devices

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### Genuair (dry powder inhalers)




*Usual Dose: 2 inhalations twice daily\*\**

<p><b>Double Genuair</b> acetylsalicylic acid 400 mcg / formoterol 12 mcg per actuation</p> 	<p><b>Tudora Genuair</b> acetylsalicylic acid 400 mcg per actuation</p> 	<p><b>Safety Considerations and Counselling Tip:</b></p> <ul style="list-style-type: none"> <li>• To prepare for inhalation, the coloured button should be pressed and then released. The coloured control window will change from red to green when the dose is ready to be inhaled. Do not hold down the button while inhaling.**</li> <li>• During dose inhalation, there is an audible "click". Close device immediately after the dose the coloured control window will change back to red. Keep breathing in even after the "click" to ensure delivery of the full dose.**</li> <li>• When a red control band appears in the dose window, obtain a new inhaler. The device will "click" when the last dose has been loaded.**</li> <li>• Some patients experience an unpleasant taste - rinse mouth and swallow water.</li> </ul>
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### Respimat (soft mist inhalers)

*Usual Dose: 2 inhalations daily\*\**

<p><b>Combivent Respimat</b> tiotropium 20 mcg / salbutamol 100 mcg per actuation</p> 	<p><b>Inspirio Respimat</b> tiotropium 2.5 mcg / salbutamol 2.5 mcg per actuation</p> 	<p><b>Spiriva Respimat</b> tiotropium 2.5 mcg per actuation</p> 	<p><b>Safety Considerations and Counselling Tip:</b></p> <ul style="list-style-type: none"> <li>• Insertion of the cartridge before first use may require more force than expected; cartridges should be pre-soaked by the pharmacy before dispensing.</li> <li>• Priming is required before first use.**</li> <li>• Before entering the device, the tip should be tightly closed over the mouthpiece without covering the air vents (on the sides of the mouthpiece).**</li> <li>• When approximately 1/2 dose supply of medication remains in the device, the red pointer will enter the red zone of the dose counter on the base.**</li> <li>• Spiriva is also available in a DPI format (Handihaler) that delivers a different dose.**</li> </ul>
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[https://www.ismp-canada.org/download/safetyBulletins/2016/ISMPCSB2016-03\\_InhalationDevices.pdf](https://www.ismp-canada.org/download/safetyBulletins/2016/ISMPCSB2016-03_InhalationDevices.pdf)