

Tripling out on COPD:

The texture of COPD trials

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disclosures

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short acting beta agonists (SABA)	
salbutamol	Ventolin MDI, Airomir MDI (generics), Ventolin Diskus
terbutaline	Bricanyl Turbuhaler
short acting muscarinic antagonists (SAMA)	
ipratropium	Atrovent MDI
short acting beta agonist + muscarinic antagonist (SAMA+SABA)	
Ipratropium + salbutamol	Combivent Respimat

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

long acting beta agonists (LABA)	
formoterol	Foradil Aerolizer
indacaterol	Onbrez Breezhaler
salmeterol	Serevent Diskus, Serevent Diskhaler
long acting muscarinic antagonist (LAMA)	
acridinium	Tudorza Genuair
glycopyrronium	Seebri Breezhaler
tiotropium	Spiriva HandiHaler, Spiriva Respimat
umeclidinium	Incruse Ellipta
dual long acting bronchodilators (LAMA+LABA)	
acridinium + formoterol	Duaklir Genuair
glycopyrronium + indacaterol	Ultibro Breezhaler
tiotropium + olodaterol	Inspiroto Respimat
umeclidinium + vilanterol	Anoro Ellipta

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

inhaled corticosteroid + long acting beta agonist (ICS + LABA)	
budesonide + formoterol	Symbicort Turbuhaler
fluticasone propionate + salmeterol	Advair Diskus, Advair MDI
fluticasone furoate + vilanterol	Breo Ellipta
triple therapy (ICS+LABA+LAMA)	
fluticasone furoate + vilanterol + umeclidinium	Trelegy Ellipta

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

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 ≥ 4
 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 ≥ 4
 1 in 7 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/>

Global Initiative for Chronic Obstructive Lung Disease
 GOLD 2018 guidelines

for symptoms	to reduce exacerbations
any bronchodilator	LAMA
↓	↓
LAMA or LABA	LAMA+LABA
↓	↓
LAMA+LABA	ICS+LABA+LAMA

<https://goldcopd.org/>

2014 Cochrane Systematic Review
Tiotropium versus placebo

numbers of people with an exacerbation
 44 per 100 (placebo) → 38 per 100
 estimate NNT 16 over one year
 ●●●●●●●●●●●●●●●●

all cause mortality
 OR 0.98 (95%CI 0.86 to 1.11)
 (23,309 participants; 22 trials)

KARNER COCHRANE 2014 CD009285

Global Initiative for Chronic Obstructive Lung Disease
 GOLD 2018 guidelines

for symptoms	to reduce exacerbations
any bronchodilator	LAMA
↓	↓
LAMA or LABA	LAMA+LABA
↓	↓
LAMA+LABA	ICS+LABA+LAMA

<https://goldcopd.org/>

Counting, analysing and reporting exacerbations of COPD in randomised controlled trials

S D Aaron,¹ D Fergusson,¹ G B Marks,² S Suissa,⁴ K L Vandemheen,¹ S Doucette,¹ F Maltais,³ J F Bourbeau,⁴ R S Goldstein,³ M Balter,⁵ D O'Donnell,⁶ M FitzGerald,⁷ for the Canadian Thoracic Society/Canadian Respiratory Clinical Research Consortium

clinical trials have not been consistent in how they count, record or analyse COPD exacerbations and methodological errors in the assessment of COPD exacerbations may lead to biased or spurious results

AARON Thorax 2008;63:122-128

SPARK 2013 (LAMA+LABA vs LAMA)

2224 participants with ≥ 1 exacerbation in previous year
 mean age 63; 25% women; 82% White; 38% current smokers
 trial duration: 1.2 years

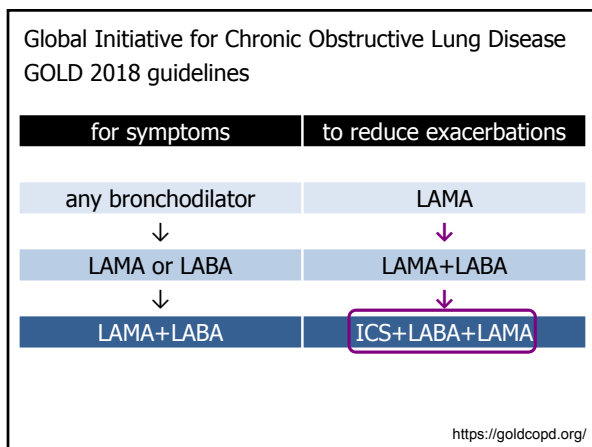
LAMA+LABA	LAMA	LAMA
glycopyrronium + indacaterol	glycopyrronium	tiotropium
ULTIBRO Breezhaler	SEEBRI Breezhaler	SPIRIVA HandiHaler
moderate or severe exacerbations (annual rate)		
0.84	0.95	0.93
vs. glycopyrronium rate ratio 0.88 (95%CI 0.77 to 0.99) ↓ 0.11 exacerbation per year		vs. tiotropium rate ratio 0.90 (0.79 to 1.02)
severe exacerbations (annual rate)		
0.09	0.12	0.08

WEDZICHA Lancet Respir Med 2013;1:199-209

SPARK 2013

glycopyrronium + indacaterol	glycopyrronium	tiotropium
serious adverse events		
23%	24%	22%
COPD worsening		
15%	16%	12%

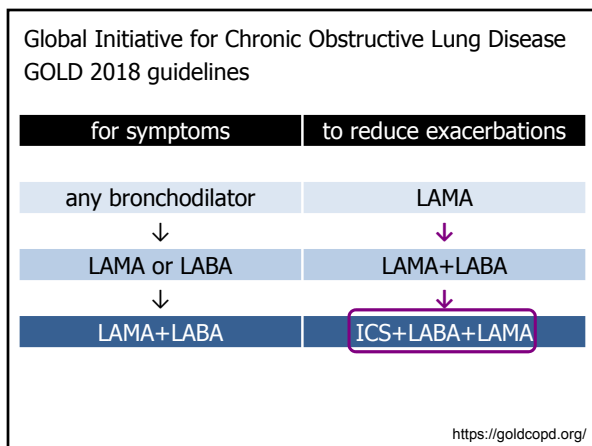
WEDZICHA Lancet Respir Med 2013;1:199-209



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 with ≥ 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

IMPACT NEJM 2018;378:1671-1680

IMPACT 2018 (triple vs. double combination therapy)		
10,355 participants; trial duration: 52 weeks		
symptomatic with ≥ 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 are 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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10,355 participants; trial duration: 52 weeks		
symptomatic with ≥ 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
moderate – severe exacerbations (annual rate)		
0.91	1.07	1.21
triple vs ICS+LABA \downarrow 0.16 exacerbation per year rate ratio 0.85 (95%CI 0.80 to 0.90)		triple versus LAMA+LABA \downarrow 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 while receiving investigational medication (ie, "on-treatment")
IMPACT NEJM 2018;378:1671-1680

IMPACT 2018 (triple vs. double combination therapy)		
10,355 participants; trial duration = 52 weeks		
symptomatic with ≥ 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
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
missing data: 20%	missing data: 27%	missing data: 29%
IMPACT NEJM 2018;378:1671-1680		

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/>

IMPACT 2018 (triple vs. double combination therapy)		
10,355 participants; trial duration: 52 weeks		
symptomatic with ≥ 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
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		
IMPACT NEJM 2018;378:1671-1680		

Safe Use of Newer Inhalation Devices





Breezhaler (dry powder inhalers)

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

<p>Onbrex Breezhaler indacaterol 75 mcg per capsule</p> 	<p>Safety Considerations and Counselling Tip:</p> <ul style="list-style-type: none"> • 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. • If swallowed by accident, skip the dose. • 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. • 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. • Closed the capsule directly into the garbage without touching. Wash hands.
<p>Serdex Breezhaler glycopyrronium 50 mcg per capsule</p> 	
<p>Vibrona Breezhaler indacaterol 110 mcg / glycopyrronium 50 mcg per capsule</p> 	

Ellipta (dry powder inhalers)

*Usual Dose: 1 inhalation daily***



<p>Anoro Ellipta fluticasone 4.2 mcg / vilanterol 25 mcg per actuation</p> 	<p>Aerolyte Ellipta fluticasone 100 or 200 mcg per actuation</p> 	<p>Safety Considerations and Counselling Tip:</p> <ul style="list-style-type: none"> • The foil packaging and desiccant must be discarded immediately after opening.** • The coloured cap should be opened before inhaling the dose. There is an audible "click" when the dose is ready to be inhaled.** • 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. • If the device is tipped past horizontal, medication can fall out of the mouthpiece. • When there are less than 10 doses remaining, the left half of the counter shows red.
<p>Breo Ellipta fluticasone 100 or 200 mcg / vilanterol 25 mcg per actuation</p> 	<p>Incorea Ellipta formoterol 4.2 mcg per actuation</p> 	

https://www.ismp-canada.org/download/safetyBulletins/2016/ISMPSCSB2016-03_InhalationDevices.pdf

Safe Use of Newer Inhalation Devices




Genuair (dry powder inhalers)

*Usual Dose: 2 inhalations twice daily***

<p>Double Genuair acetylsalicylic acid 400 mcg / formoterol 12 mcg per actuation</p> 	<p>Tudora Genuair acetylsalicylic acid 400 mcg per actuation</p> 	<p>Safety Considerations and Counselling Tip:</p> <ul style="list-style-type: none"> • 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.** • During dose inhalation, there is an audible "click". Close device inhalation of 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.** • 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.** • Some patients experience an unpleasant taste - rinse mouth and swallow water.
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Respimat (soft mist inhalers)

*Usual Dose: 2 inhalations daily***

<p>Combivent Respimat tiotropium 20 mcg / salbutamol 100 mcg per actuation</p> 	<p>Inspirio Respimat tiotropium 2.5 mcg / salbutamol 2.5 mcg per actuation</p> 	<p>Spiro Respimat tiotropium 2.5 mcg per actuation</p> 	<p>Safety Considerations and Counselling Tip:</p> <ul style="list-style-type: none"> • Insertion of the cartridge before first use may require more force than expected; cartridges should be preloaded by the pharmacy before dispensing. • Pre-rinsing is required before first use.** • Before entering the device, the tip should be tightly closed over the mouthpiece without covering the air vents (on the sides of the mouthpiece).** • 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.** • Spiro is also available in a DPI format (Handihaler) that delivers a different dose.**
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https://www.ismp-canada.org/download/safetyBulletins/2016/ISMPSCSB2016-03_InhalationDevices.pdf