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)	
aclidinium	Tudorza *Genuair*
glycopyrronium	Seebri *Breezhaler*
tiotropium	Spiriva *HandiHaler*, Spiriva *Respimat*
umeclidinium	Incruse *Ellipta*
dual long acting bronchodilators (LAMA+LABA)	
aclidinium + formoterol	Duaklir *Genuair*
glycopyrronium + indacaterol	Ultibro *Breezhaler*
tiotropium + olodaterol	Inspiolto *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,[5] 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

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GOLD 2018 guidelines

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↓	↓
LAMA or LABA	LAMA+LABA
↓	↓
LAMA+LABA	ICS+LABA+LAMA

https://goldcopd.org/

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

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/

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

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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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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 while receiving investigational medication (ie, "on-treatment")

IMPACT NEJM 2018;378:1671-1680

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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/

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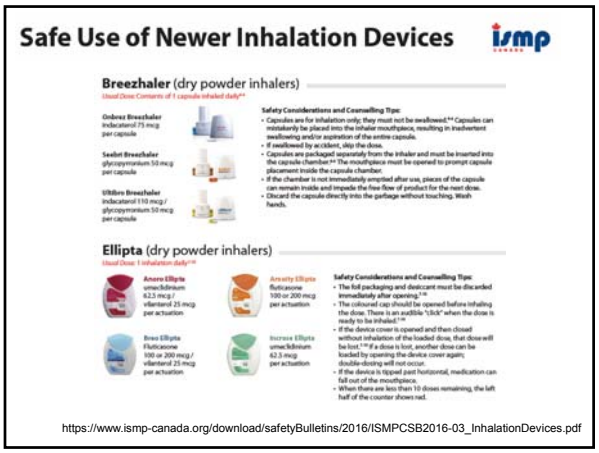
symptomatic with ≥ 1 exacerbation in previous year
1 = 45%; 2 = 43%; ≥ 3 = 11%

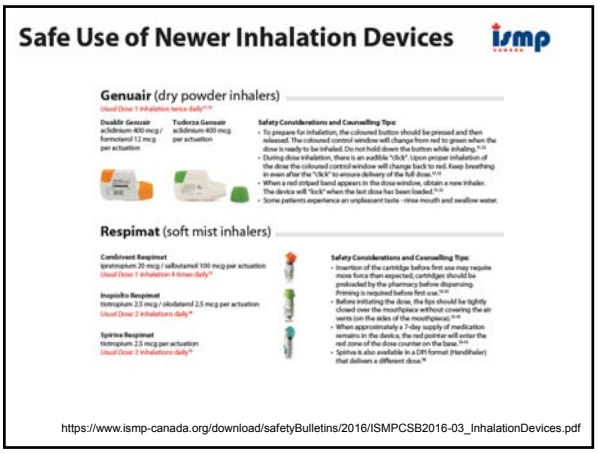
mean age 65; 34% women; 78% White

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
ismp
Breezhaler (dry powder inhalers)
Safety Considerations and Counselling Tips:
Ellipta (dry powder inhalers)
Safety Considerations and Counselling Tips:
https://www.ismp-canada.org/download/safetyBulletins/2016/ISMPCSB2016-03_InhalationDevices.pdf


Safe Use of Newer Inhalation Devices
ismp
Genuair (dry powder inhalers)
Safety Considerations and Counselling Tips:
Respimat (soft mist inhalers)
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https://www.ismp-canada.org/download/safetyBulletins/2016/ISMPCSB2016-03_InhalationDevices.pdf