KOAH’da Uzun Süreli İlaç Tedavileri ve Hasta Uyumu

Dr.Özlem Şengören Dikiş

13.12.2025

Nevşehir

KOAH'da Güncel Farmakoterapinin Odağı

Semptom ve Alevlenme Kontrolü
Kronik semptomların hafifletilmesi ve alevlenmelerin önlenmesi

FEV_1 Azalması
FEV_1'deki yıllık düşüş, hastalığın doğal seyrini izlemek için kullanılan sonlanım noktası

Farmakoterapinin FEV_1 Üzerindeki Etkisi
FEV_1 düşüş hızında belirgin bir yavaşlama henüz yok

Farmakoterapinin FEV_1 Azalma Hızına Etkisi

Clinical Trial > Lancet. 1999 May 29;353(9167):1819-23. doi: 10.1016/s0140-6736(98)10019-3.

Long-term effect of inhaled budesonide in mild and moderate chronic obstructive pulmonary disease: a randomised controlled trial

J Vestbo [1], T Sørensen, P Lange, A Brix, P Torre, K Viskum

Affiliations + expand

PMID: 10359405 DOI: 10.1016/s0140-6736(98)10019-3

Abstract

Klinik çalışmalar, yeterli güçte ve sonuç verici değil

capacity of 0.7 or less; FEV1 which showed no response (<15% change) to 1 mg inhaled terbutaline or prednisolone 37.5 mg orally once daily for 10 days. 290 patients were randomly assigned budesonide, 800 microg plus 400 microg daily for 6 months followed by 400 microg twice daily for 30 months, or placebo for 36 months. The mean age of the participants was 59 years and the mean FEV1 2.37 L or 86% of predicted. The main outcome measure was rate of FEV1 decline. Analyses were by intention to treat.

Findings: The crude rates of FEV1 decline were slightly smaller than expected (placebo group 41.8 mL per year, budesonide group 45.1 mL per year). The estimated rates of decline from the regression model did not differ significantly (49.1 mL vs 46.0 mL per year; difference 3.1 mL per year [95% CI -12.8 to 19.0]; p=0.7). Before the study, the minimum relevant difference was defined as 20 mL per year; this difference was outside the 95% CI. No effect of inhaled budesonide was seen on respiratory

> Am J Respir Crit Care Med. 2021 Mar 15;203(6):689-698. doi: 10.1164/rccm.202005-1854OC.

Pharmacotherapy and Lung Function Decline in Patients with Chronic Obstructive Pulmonary Disease. A Systematic Review

Bartolome R Celli [1], Julie A Anderson [2], Nicholas J Cowans [3], Courtney Crim [4], Benjamin F Hartley [3], Fernando J Martinez [5], Andrea N Morris [4], Holly Quasny [4], Julie Yates [4], Jørgen Vestbo [6], Peter M A Calverley [7]

FEV_1 azalma hızı

-5,0 mL /yıl

Uzun etkili bronkodilatör (LABA/LAMA)

–4,9 mL/yıl fark

İnhale kortikosteroid (ICS)

–7,3 mL/yıl fark

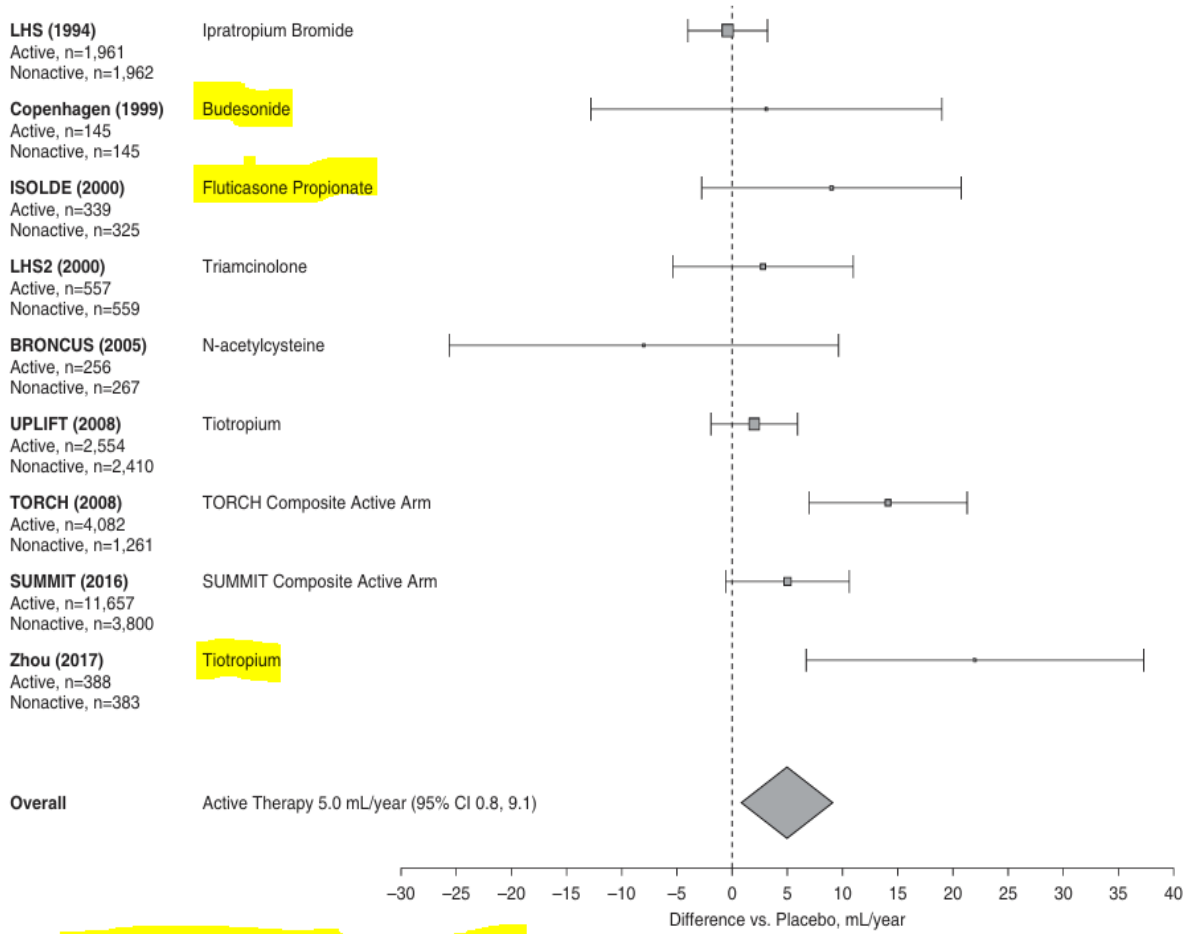

Figure 2. Effect of all active therapies on the rate of decline in FEV_1. The center of the diamond indicates the point estimate and the width is the 95% CI. BRONCUS = Bronchitis Randomized on NAC Cost-Utility Study; CI = confidence interval; COPD = chronic obstructive pulmonary disease; ISOLDE = Inhaled Steroids in Obstructive Lung Disease in Europe; LHS = Lung Health Study; LHS2 = Lung Health Study 2; SUMMIT = Study to Understand Mortality and Morbidity; TORCH = Toward a Revolution in COPD Health; UPLIFT = Understanding Potential Long-Term Impacts on Function with Tiotropium.

Table 2. Impact of Therapy on FEV_1, in the Studies Included in This Systematic Review

	(1997–2003) BRONCUS* Ref 16	(1992–1998) ISOLDE* Ref 6	(2000–2005) TORCH* Ref 18	(2003–2008) UPLIFT* Ref 11	(1986–1994) Lung Health I* Ref 3	(2011–2015) Zhou *et al.** Ref 19	(2011–2015) SUMMIT* Refs 12 and 20	(1992–1994) Copenhagen City Lung Study* Ref 17	(1994–1999) Lung Health Triamcinolone* Ref 21
Treatment arms: placebo/**active intervention**	Placebo/***N*-acetylcysteine**	Placebo/**fluticasone propionate**	Placebo/**salmeterol/fluticasone propionate/**	Placebo/**tiotropium**	Placebo/**ipratropium bromide**	Placebo/**tiotropium**	Placebo/**fluticasone furoate/vilanterol/fluticasone**	Placebo/**budesonide**	Placebo/**triamcinolone acetonide**
			39.0 (3.0)/ *41.2 (1.8)*				38 (2.4)/ *41 (1.4)*		
Treatment difference for each active arm vs. placebo (SE) [95% CI], ml	−8 (9.0) [−25 to 10]	9 (6.0) [−3 to 20]	13.0 (4.4) [4.3 to 21.7]/ 13.0 (4.4) [4.3 to 21.7]/ 16.3 (4.4) [7.7 to 24.9]/ *14.1 (3.7) [7.0 to 21.3]*	2 (2) [−2 to 6]	−4 (1.8)	22 (7.8) [6 to 37]	8 (3.5) [1 to 14]/ −2 (3.4) [−8 to 5]/ 8 (3.4) [1 to 15]/ *5 (2.9) [−1 to 11]*	3.1 (8.1) [−12.8 to 19.0]	2.8 (4.2)

FEV_1 azalma hızı farmakoterapi ile kısmen modifiye

KOAH'ta İdame Tedaviler

Generic Drug Name	Inhaler Type	Nebulizer	Oral/Injectable Delivery	Duration of Action
BETA$_2$-Agonists				
Short-acting (SABA)				
Fenoterol	MDI	✓	tablet, solution	variable
Levalbuterol	MDI	✓		variable
Salbutamol (albuterol)	MDI, DPI	✓	syrup, tablet	variable
Terbutaline	DPI		tablet	variable
Long-acting (LABA)				
Arformoterol		✓		12 hours
Formoterol	DPI	✓		12 hours
Indacaterol	DPI			24 hours
Olodaterol	SMI			24 hours
Salmeterol	MDI, DPI			12 hours
Anticholinergics				
Short-acting (SAMA)				
Ipratropium bromide	MDI	✓		6-8 hours
Oxitropium bromide	MDI	✓		7-9 hours
Long-acting (LAMA)				
Aclidinium bromide	DPI			12 hours
Glycopyrronium bromide	DPI	✓	solution	variable
Tiotropium	DPI, SMI, MDI			24 hours
Umeclidinium	DPI			24 hours
Revefenacin		✓		24 hours
Combination Short-Acting Beta$_2$-Agonist Plus Anticholinergic in One Device (SABA+SAMA)				
Fenoterol/ipratropium	SMI	✓		6-8 hours
Salbutamol/ipratropium	SMI, MDI	✓		variable
Combination Long-Acting Beta$_2$-Agonist Plus Anticholinergic in One Device (LABA+LAMA)				
Formoterol/aclidinium	DPI			12 hours
Formoterol/glycopyrronium	MDI			12 hours
Indacaterol/glycopyrronium	DPI			12-24 hours
Vilanterol/umeclidinium	DPI			24 hours
Olodaterol/tiotropium	SMI			24 hours
Methylxanthines				
Aminophylline			solution, injectable	variable
Theophylline (SR)			tablet, capsule, elixir, solution, injectable	variable
Combination of Long-Acting Beta$_2$-Agonist Plus Corticosteroid in One Device (LABA+ICS)				
Formoterol/beclometasone	MDI, DPI			12 hours
Formoterol/budesonide	MDI, DPI			12 hours
Formoterol/mometasone	MDI			12 hours
Salmeterol/fluticasone propionate	MDI, DPI			12 hours
Vilanterol/fluticasone furoate	DPI			24 hours
Triple Combination in One Device (LABA+LAMA+ICS)				
Fluticasone/umeclidinium/vilanterol	DPI			24 hours
Beclometasone/formoterol/glycopyrronium	MDI, DPI			12 hours
Budesonide/formoterol/glycopyrrolate	MDI			12 hours
Phosphodiesterase-3 and/or -4 Inhibitors				
Roflumilast			tablet	24 hours
Ensifentrine		✓		12 hours
Mucolytic Agents				
Erdosteine			capsule, suspension	12 hours
Carbocysteine†			capsule, packet, solution, syrup	6-8 hours
N-acetylcysteine†		✓	solution, tablet	2-6 hours
Biologics				
Dupilumab			injectable	2 weeks
Mepolizumab			injectable	4 weeks

*This list is not exhaustive. Not all formulations are available in all countries. In some countries other formulations and dosages may be available. †Dosing regimens are under discussion. MDI = metered dose inhaler; DPI = dry powder inhaler; SMI = soft mist inhaler. Note that glycopyrrolate & glycopyrronium are the same compound.

Stabil KOAH'ta Bronkodilatörler

- Inhaled bronchodilators in COPD are central to symptom management and commonly given on a regular basis to prevent or reduce symptoms **(Evidence A)**
- Inhaled bronchodilators are recommended over oral bronchodilators (**Evidence A**)
- Regular and as-needed use of SABA or SAMA improves FEV1 and symptoms **(Evidence A)**
- Combinations of SABA and SAMA are superior compared to either medication alone in improving FEV1 and symptoms **(Evidence A)**
- LABAs and LAMAs are preferred over short-acting agents except for patients with only occasional dyspnea (**Evidence A**), and for immediate relief of symptoms in patients already on long-acting bronchodilators for maintenance therapy
- LABAs and LAMAs significantly improve lung function, dyspnea, health status, and reduce exacerbation rates **(Evidence A)**
- LAMAs have a greater effect on exacerbation reduction compared with LABAs **(Evidence A)** and decrease hospitalizations **(Evidence B)**
- When initiating treatment with long acting bronchodilators the preferred choice is a combination of a LABA and a LAMA. In patients with persistent dyspnea on a single long-acting bronchodilator treatment should be escalated to two (**Evidence A**).
- Combination treatment with a LABA and a LAMA increases FEV1 and reduces symptoms compared to monotherapy **(Evidence A)**
- Combination treatment with a LABA+LAMA reduces exacerbations compared to monotherapy **(Evidence B)**
- Combinations can be given as single inhaler or multiple inhaler treatment. Single inhaler therapy may be more convenient and effective than multiple inhalers
- Ensifentrine significantly improves lung function **(Evidence A)**, dyspnea **(Evidence A)** and health status **(Evidence B)**
- Theophylline exerts a small bronchodilator effect in stable COPD **(Evidence A)** and that is associated with modest symptomatic benefits **(Evidence B)**

Hava yolu düz kas tonusunu değiştirir
FEV_1 ve semptomları iyileştirir

β_2-agonistler

Kısa Etkili β_2-agonistler (SABA)

Uzun Etkili β_2-agonistler(LABA)

KOAH'ta İdame Tedaviler

Generic Drug Name	Inhaler Type	Nebulizer	Oral/Injectable Delivery	Duration of Action
BETA$_2$-Agonists				
Short-acting (SABA)				
Fenoterol	MDI	✓	tablet, solution	variable
Levalbuterol	MDI	✓		variable
Salbutamol (albuterol)	MDI, DPI	✓	syrup, tablet	variable
Terbutaline	DPI		tablet	variable
Long-acting (LABA)				
Arformoterol		✓		12 hours
Formoterol	DPI	✓		12 hours
Indacaterol	DPI			24 hours
Olodaterol	SMI			24 hours
Salmeterol	MDI, DPI			12 hours
Anticholinergics				
Short-acting (SAMA)				
Ipratropium bromide	MDI	✓		6-8 hours
Oxitropium bromide	MDI	✓		7-9 hours
Long-acting (LAMA)				
Aclidinium bromide	DPI			12 hours
Glycopyrronium bromide	DPI	✓	solution	variable
Tiotropium	DPI, SMI, MDI			24 hours
Umeclidinium	DPI			24 hours
Revefenacin		✓		24 hours
Combination Short-Acting Beta$_2$-Agonist Plus Anticholinergic in One Device (SABA+SAMA)				
Fenoterol/ipratropium	SMI	✓		6-8 hours
Salbutamol/ipratropium	SMI, MDI	✓		variable
Combination Long-Acting Beta$_2$-Agonist Plus Anticholinergic in One Device (LABA+LAMA)				
Formoterol/aclidinium	DPI			12 hours
Formoterol/glycopyrronium	MDI			12 hours
Indacaterol/glycopyrronium	DPI			12-24 hours
Vilanterol/umeclidinium	DPI			24 hours
Olodaterol/tiotropium	SMI			24 hours
Methylxanthines				
Aminophylline			solution, injectable	variable
Theophylline (SR)			tablet, capsule, elixir, solution, injectable	variable
Combination of Long-Acting Beta$_2$-Agonist Plus Corticosteroid in One Device (LABA+ICS)				
Formoterol/beclometasone	MDI, DPI			12 hours
Formoterol/budesonide	MDI, DPI			12 hours
Formoterol/mometasone	MDI			12 hours
Salmeterol/fluticasone propionate	MDI, DPI			12 hours
Vilanterol/fluticasone furoate	DPI			24 hours
Triple Combination in One Device (LABA+LAMA+ICS)				
Fluticasone/umeclidinium/vilanterol	DPI			24 hours
Beclometasone/formoterol/glycopyrronium	MDI, DPI			12 hours
Budesonide/formoterol/glycopyrrolate	MDI			12 hours
Phosphodiesterase-3 and/or -4 Inhibitors				
Roflumilast			tablet	24 hours
Ensifentrine		✓		12 hours
Mucolytic Agents				
Erdosteine			capsule, suspension	12 hours
Carbocysteine†			capsule, packet, solution, syrup	6-8 hours
N-acetylcysteine†		✓	solution, tablet	2-6 hours
Biologics				
Dupilumab			injectable	2 weeks
Mepolizumab			injectable	4 weeks

*This list is not exhaustive. Not all formulations are available in all countries. In some countries other formulations and dosages may be available. †Dosing regimens are under discussion. MDI = metered dose inhaler; DPI = dry powder inhaler; SMI = soft mist inhaler. Note that glycopyrrolate & glycopyrronium are the same compound.

Main results

Thirteen studies were included in this review. All studies used a crossover design and were of high quality. Spirometry performed at the end of the study period and after the administration of treatment (post-bronchodilator) showed a slight but significant increase in FEV1 and FVC when compared to placebo (WMD 0.14 L; 95%CI 0.04, 0.25 & WMD 0.30 L; 95%CI 0.02, 0.58, respectively). In addition, both morning and evening PEFR were significantly better during active treatment than during placebo (WMD 29.17 L/min; 95%CI 0.25, 58.09 & WMD 36.75 L/min; 95%CI 2.56, 70.94, respectively).

A significant improvement in daily breathlessness score was observed during treatment with beta-2 agonist when compared to placebo (SMD 1.33; 95%CI 1.0, 1.65).

SABA
Etki süresi 4–6 saat
FEV_1 /semptomlarda iyileşme sağlar

Sestini P et al.Cochrane Database Syst Rev. 2002;(4):CD001495. doi: 10.1002/14651858.CD001495.

Antimuskarinik İlaçlar (SAMA / LAMA)

KOAH'ta İdame Tedaviler

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BETA$_2$-Agonists				
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Fenoterol	MDI	✓	tablet, solution	variable
Levalbuterol	MDI	✓		variable
Salbutamol (albuterol)	MDI, DPI	✓	syrup, tablet	variable
Terbutaline	DPI		tablet	variable
Long-acting (LABA)				
Arformoterol		✓		12 hours
Formoterol	DPI	✓		12 hours
Indacaterol	DPI			24 hours
Olodaterol	SMI			24 hours
Salmeterol	MDI, DPI			12 hours
Anticholinergics				
Short-acting (SAMA)				
Ipratropium bromide	MDI	✓		6-8 hours
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Revefenacin		✓		24 hours
Combination Short-Acting Beta$_2$-Agonist Plus Anticholinergic in One Device (SABA+SAMA)				
Fenoterol/ipratropium	SMI	✓		6-8 hours
Salbutamol/ipratropium	SMI, MDI	✓		variable
Combination Long-Acting Beta$_2$-Agonist Plus Anticholinergic in One Device (LABA+LAMA)				
Formoterol/aclidinium	DPI			12 hours
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Indacaterol/glycopyrronium	DPI			12-24 hours
Vilanterol/umeclidinium	DPI			24 hours
Olodaterol/tiotropium	SMI			24 hours
Methylxanthines				
Aminophylline			solution, injectable	variable
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SAMA-İpratropium

- **FEV1'de**
- **Oral steroid gereksiniminde SABA'ya göre daha anlamlı farklılık sağlar**

Appleton S, et al.Ipratropium bromide versus long-acting beta-2 agonists for stable chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2006 Jul 19;2006(3):CD006101. doi: 10.1002/14651858.CD006101

LAMA
Tiotropium, aklidinyum, glikoppironyum bromür (glikoppirolat), umeklidinyum, revefenacin

Doz Sıklığı

Günde 1 kez
Tiotropium, umeklidinyum, revefenacin

Günde 2 kez
Bazı aklidinyum ve glikoppirrolat formları

Her iki kullanım şekli
Glikopirrolat (ülkeye göre değişen onaylarla)

Melani AS. Long-acting muscarinic antagonists. Expert Rev Clin Pharmacol. 2015;8(4):479-501. doi: 10.1586/17512433.2015.1058154.

Stabil KOAH'ta Bronkodilatörler

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- Combinations can be given as single inhaler or multiple inhaler treatment. Single inhaler therapy may be more convenient and effective than multiple inhalers
- Ensifentrine significantly improves lung function **(Evidence A)**, dyspnea **(Evidence A)** and health status **(Evidence B)**
- Theophylline exerts a small bronchodilator effect in stable COPD **(Evidence A)** and that is associated with modest symptomatic benefits **(Evidence B)**

Tiotropium LABA tedavisine kıyasla alevlenme oranlarını daha belirgin azalttır

Yan Etki/Güvenlilik Profili

Zayıf sistemik emilim

- **Atropine benzer sistemik yan etkilerin ortaya çıkma olasılığı düşük**

Geniş doz aralıklarında kullanım

- **Yüksek güvenlilik profili**

Melani AS. Expert Rev Clin Pharmacol. 2015;8(4):479-501. doi: 10.1586/17512433.2015.1058154

Tashkin DP. Curr Opin Pulm Med. 2010 Mar;16(2):97-105. doi: 10.1097/MCP.0b013e328335df1e.

Table 3—*Serious, Including Fatal, Selected Adverse Events From Pooled Placebo-Controlled Trials

Selected Events	Tiotropium No.	Tiotropium Person-Years	Tiotropium Rate†	Placebo No.	Placebo Person-Years	Placebo Rate†	95% CI RR	95% CI Lower	95% CI Upper
Total treated	4,435	2,172		3,384	1,672	NA	NA	NA	NA
Fatal adverse events									
Total deaths	42	2,168	1.94	46	1,668	2.76	0.76	0.50	1.16
Fatal cardiovascular events	11	2,171	0.51	16	1,671	0.96	0.57	0.26	1.26
Cardiac arrest	4	2,171	0.18	7	1,671	0.42	0.50	0.14	1.76
Myocardial infarction	3	2,171	0.14	1	1,672	0.06	2.65	0.26	27.13

Çalışma Popülasyonu
Tiotropium: 4.435 hasta
Plasebo: 3.384 hasta

- **Ağız kuruluğu en sık**
- **Üriner retansiyon riski belirgin artmış**

Diğer advers olaylar hafif–orta düzeyde

Hyperglycemia	3	2,171	0.14	0	1,672	0.00	∞	0.32	∞
Renal and urinary disorders									
Prostatic disorder	6	2,169	0.28	1	1,672	0.06	5.32	0.59	48.33
Renal failure	5	2,170	0.23	2	1,671	0.12	2.33	0.45	11.95
Urinary retention	3	2,171	0.14	1	1,672	0.06	2.60	0.25	26.55
Urinary tract infection	4	2,171	0.18	2	1,672	0.12	1.99	0.33	7.84
Respiratory infections									
Bronchitis infections	12	2,168	0.55	7	1,670	0.42	1.61	0.64	4.10
Pneumonia	50	2,160	2.31	66	1,658	3.98	0.60	0.41	0.87
Respiratory thoracic and mediastinal disorders									
Asthma	3	2,171	0.14	1	1,672	0.06	2.52	0.23	27.22
COPD exacerbation	152	2,138	7.11	165	1,633	10.10	0.68	0.54	0.85
Dyspnea	21	2,167	0.97	16	1,667	0.96	0.76	0.38	1.52
Respiratory failure	13	2,167	0.60	21	1,667	1.26	0.57	.029	1.13

*Data are presented for two or more selected events in patients receiving tiotropium. NA = not applicable.
†All rates are per 100 person-years.

Kesten S, Jara M, Wentworth C, Lanes S. Chest. 2006 Dec;130(6):1695-703. doi: 10.1378/chest.130.6.1695.

N Engl J Med. 2010 Sep 16;363(12):1097-9. doi: 10.1056/NEJMp1008502. Epub 2010 Sep 8.

The safety of tiotropium--the FDA's conclusions

Theresa M Michele [1], Simone Pinheiro, Solomon Iyasu

Safety Data from Pooled Analysis of Tiotropium Trials and UPLIFT.*

Attribute	29 Pooled Trials (N=13,544)	UPLIFT (N=5992)
Study duration	1–12 mo	48 mo
Patient-years (placebo group)	3065	8499
Patient-years (tiotropium group)	4571	9222
Relative risk (95% CI)		
Stroke	1.37 (0.73–15.6)	0.95 (0.70–1.29)
Myocardial infarction		0.71 (0.51–0.99)
Death from cardiovascular causes†	0.97 (0.54–1.75)	0.73 (0.56–0.95)
Death from any cause		0.85 (0.74–0.98)

UPLİFT çalışması
Tiotropium kardiyovasküler risk üzerinde artırıcı bir etkisi yok

cardiac death, or sudden cardiac death.

METİLKSANTİNLER

KOAH'ta İdame Tedaviler

Figure A3.1

Generic Drug Name	Inhaler Type	Nebulizer	Oral/Injectable Delivery	Duration of Action
BETA$_2$-Agonists				
Short-acting (SABA)				
Fenoterol	MDI	✓	tablet, solution	variable
Levalbuterol	MDI	✓		variable
Salbutamol (albuterol)	MDI, DPI	✓	syrup, tablet	variable
Terbutaline	DPI		tablet	variable
Long-acting (LABA)				
Arformoterol		✓		12 hours
Formoterol	DPI	✓		12 hours
Indacaterol	DPI			24 hours
Olodaterol	SMI			24 hours
Salmeterol	MDI, DPI			12 hours
Anticholinergics				
Short-acting (SAMA)				
Ipratropium bromide	MDI	✓		6-8 hours
Oxitropium bromide	MDI	✓		7-9 hours
Long-acting (LAMA)				
Aclidinium bromide	DPI			12 hours
Glycopyrronium bromide	DPI	✓	solution	variable
Tiotropium	DPI, SMI, MDI			24 hours
Umeclidinium	DPI			24 hours
Revefenacin		✓		24 hours
Combination Short-Acting Beta$_2$-Agonist Plus Anticholinergic in One Device (SABA+SAMA)				
Fenoterol/ipratropium	SMI	✓		6-8 hours
Salbutamol/ipratropium	SMI, MDI	✓		variable
Combination Long-Acting Beta$_2$-Agonist Plus Anticholinergic in One Device (LABA+LAMA)				
Formoterol/aclidinium	DPI			12 hours
Formoterol/glycopyrronium	MDI			12 hours
Indacaterol/glycopyrronium	DPI			12-24 hours
Vilanterol/umeclidinium	DPI			24 hours
Olodaterol/tiotropium	SMI			24 hours
Methylxanthines				
Aminophylline			solution, injectable	variable
Theophylline (SR)			tablet, capsule, elixir, solution, injectable	variable
Combination of Long-Acting Beta$_2$-Agonist Plus Corticosteroid in One Device (LABA+ICS)				
Formoterol/beclometasone	MDI, DPI			12 hours
Formoterol/budesonide	MDI, DPI			12 hours
Formoterol/mometasone	MDI			12 hours
Salmeterol/fluticasone propionate	MDI, DPI			12 hours
Vilanterol/fluticasone furoate	DPI			24 hours
Triple Combination in One Device (LABA+LAMA+ICS)				
Fluticasone/umeclidinium/vilanterol	DPI			24 hours
Beclometasone/formoterol/glycopyrronium	MDI, DPI			12 hours
Budesonide/formoterol/glycopyrrolate	MDI			12 hours
Phosphodiesterase-3 and/or -4 Inhibitors				
Roflumilast			tablet	24 hours
Ensifentrine		✓		12 hours
Mucolytic Agents				
Erdosteine			capsule, suspension	12 hours
Carbocysteine†			capsule, packet, solution, syrup	6-8 hours
N-acetylcysteine†		✓	solution, tablet	2-6 hours
Biologics				
Dupilumab			injectable	2 weeks
Mepolizumab			injectable	4 weeks

*This list is not exhaustive. Not all formulations are available in all countries. In some countries other formulations and dosages may be available. †Dosing regimens are under discussion. MDI = metered dose inhaler; DPI = dry powder inhaler; SMI = soft mist inhaler. Note that glycopyrrolate & glycopyrronium are the same compound.

Stabil KOAH'ta Bronkodilatörler

- Inhaled bronchodilators in COPD are central to symptom management and commonly given on a regular basis to prevent or reduce symptoms **(Evidence A)**
- Inhaled bronchodilators are recommended over oral bronchodilators (**Evidence A**)
- Regular and as-needed use of SABA or SAMA improves FEV1 and symptoms **(Evidence A)**
- Combinations of SABA and SAMA are superior compared to either medication alone in improving FEV1 and symptoms **(Evidence A)**
- LABAs and LAMAs are preferred over short-acting agents except for patients with only occasional dyspnea (**Evidence A**), and for immediate relief of symptoms in patients already on long-acting bronchodilators for maintenance therapy
- LABAs and LAMAs significantly improve lung function, dyspnea, health status, and reduce exacerbation rates **(Evidence A)**
- LAMAs have a greater effect on exacerbation reduction compared with LABAs **(Evidence A)** and decrease hospitalizations **(Evidence B)**
- When initiating treatment with long acting bronchodilators the preferred choice is a combination of a LABA and a LAMA. In patients with persistent dyspnea on a single long-acting bronchodilator treatment should be escalated to two (**Evidence A**).
- Combination treatment with a LABA and a LAMA increases FEV1 and reduces symptoms compared to monotherapy **(Evidence A)**
- Combination treatment with a LABA+LAMA reduces exacerbations compared to monotherapy **(Evidence B)**
- Combinations can be given as single inhaler or multiple inhaler treatment. Single inhaler therapy may be more convenient and effective than multiple inhalers
- Ensifentrine significantly improves lung function **(Evidence A)**, dyspnea **(Evidence A)** and health status **(Evidence B)**
- Theophylline exerts a small bronchodilator effect in stable COPD **(Evidence A)** and that is associated with modest symptomatic benefits **(Evidence B)**

Teofilin Stabil KOAH'ta hafif düzeyde bronkodilatör etki

Ciddi yan etkiler

- **Atrial ve ventriküler aritmiler**
- **Grand mal konvülsiyon**

Daha Sık Görülen Yan Etkiler

- **Baş ağrısı**
- **Uykusuzluk**
- **Bulantı**
- **Mide yanması**

Bu yan etkiler terapötik serum düzeylerinde bile ortaya çıkabilir!!!

Ram FS, et al.Cochrane Database Syst Rev. 2002;2002(4):CD003902. doi: 10.1002/14651858.CD003902. PMID: 12519617

Teofilin etkinliği sınırlı, yan etki potansiyeli yüksek olduğundan KOAH idame tedavisinde birinci seçenek değil!!

Kombinasyon Bronkodilatör Tedavi

KOAH'ta İdame Tedaviler

Figure A3.1

Generic Drug Name	Inhaler Type	Nebulizer	Oral/Injectable Delivery	Duration of Action
BETA$_2$-Agonists				
Short-acting (SABA)				
Fenoterol	MDI	✓	tablet, solution	variable
Levalbuterol	MDI	✓		variable
Salbutamol (albuterol)	MDI, DPI	✓	syrup, tablet	variable
Terbutaline	DPI		tablet	variable
Long-acting (LABA)				
Arformoterol		✓		12 hours
Formoterol	DPI	✓		12 hours
Indacaterol	DPI			24 hours
Olodaterol	SMI			24 hours
Salmeterol	MDI, DPI			12 hours
Anticholinergics				
Short-acting (SAMA)				
Ipratropium bromide	MDI	✓		6-8 hours
Oxitropium bromide	MDI	✓		7-9 hours
Long-acting (LAMA)				
Aclidinium bromide	DPI			12 hours
Glycopyrronium bromide	DPI	✓	solution	variable
Tiotropium	DPI, SMI, MDI			24 hours
Umeclidinium	DPI			24 hours
Revefenacin		✓		24 hours
Combination Short-Acting Beta$_2$-Agonist Plus Anticholinergic in One Device (SABA+SAMA)				
Fenoterol/ipratropium	SMI	✓		6-8 hours
Salbutamol/ipratropium	SMI, MDI	✓		variable
Combination Long-Acting Beta$_2$-Agonist Plus Anticholinergic in One Device (LABA+LAMA)				
Formoterol/aclidinium	DPI			12 hours
Formoterol/glycopyrronium	MDI			12 hours
Indacaterol/glycopyrronium	DPI			12-24 hours
Vilanterol/umeclidinium	DPI			24 hours
Olodaterol/tiotropium	SMI			24 hours
Methylxanthines				
Aminophylline			solution, injectable	variable
Theophylline (SR)			tablet, capsule, elixir, solution, injectable	variable
Combination of Long-Acting Beta$_2$-Agonist Plus Corticosteroid in One Device (LABA+ICS)				
Formoterol/beclometasone	MDI, DPI			12 hours
Formoterol/budesonide	MDI, DPI			12 hours
Formoterol/mometasone	MDI			12 hours
Salmeterol/fluticasone propionate	MDI, DPI			12 hours
Vilanterol/fluticasone furoate	DPI			24 hours
Triple Combination in One Device (LABA+LAMA+ICS)				
Fluticasone/umeclidinium/vilanterol	DPI			24 hours
Beclometasone/formoterol/glycopyrronium	MDI, DPI			12 hours
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Phosphodiesterase-3 and/or -4 Inhibitors				
Roflumilast			tablet	24 hours
Ensifentrine		✓		12 hours
Mucolytic Agents				
Erdosteine			capsule, suspension	12 hours
Carbocysteine†			capsule, packet, solution, syrup	6-8 hours
N-acetylcysteine†		✓	solution, tablet	2-6 hours
Biologics				
Dupilumab			injectable	2 weeks
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- LAMAs have a greater effect on exacerbation reduction compared with LABAs **(Evidence A)** and decrease hospitalizations **(Evidence B)**
- When initiating treatment with long acting bronchodilators the preferred choice is a combination of a LABA and a LAMA. In patients with persistent dyspnea on a single long-acting bronchodilator treatment should be escalated to two (**Evidence A**).
- Combination treatment with a LABA and a LAMA increases FEV1 and reduces symptoms compared to monotherapy **(Evidence A)**
- Combination treatment with a LABA+LAMA reduces exacerbations compared to monotherapy **(Evidence B)**
- Combinations can be given as single inhaler or multiple inhaler treatment. Single inhaler therapy may be more convenient and effective than multiple inhalers
- Ensifentrine significantly improves lung function **(Evidence A)**, dyspnea **(Evidence A)** and health status **(Evidence B)**
- Theophylline exerts a small bronchodilator effect in stable COPD **(Evidence A)** and that is associated with modest symptomatic benefits **(Evidence B)**

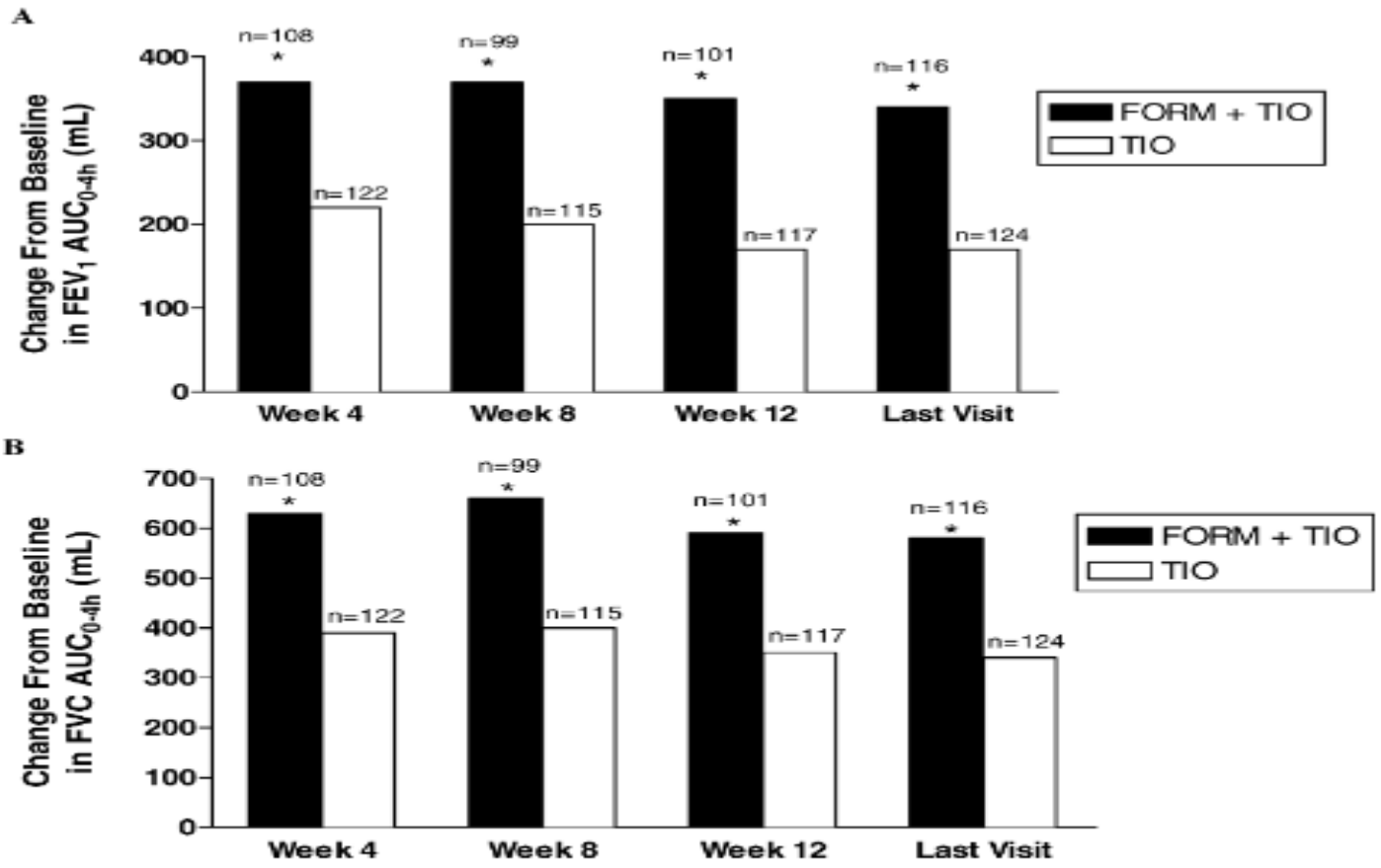

Figure 4. Improvements by treatment visit in normalized forced expiratory volume in 1 second (FEV_1) area under the response-time curve from 0–4 hours (AUC_{0-4h}) (A) and normalized forced vital capacity (FVC) AUC_{0-4h}(B). FORM = formoterol fumarate 12 μg BID; TIO = tiotropium bromide 18 μg QD. $^*p < 0.001$ compared with TIO.

SABA /SAMA ve LABA/LAMA

FEV_1 ve semptom üzerinde her ilacın tek başına kullanımına göre daha etkili!!!

Gross et al. Dey Combination Solution Study Group. Respiration. 1998;65(5):354-62. doi: 10.1159/000029295.

Tashkin,et al. COPD. 2009 Feb;6(1):17-25. doi: 10.1080/15412550902724073..

Stabil KOAH'ta Bronkodilatörler

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- Combination treatment with a LABA+LAMA reduces exacerbations compared to monotherapy **(Evidence B)**
- Combinations can be given as single inhaler or multiple inhaler treatment. Single inhaler therapy may be more convenient and effective than multiple inhalers
- Ensifentrine significantly improves lung function **(Evidence A)**, dyspnea **(Evidence A)** and health status **(Evidence B)**
- Theophylline exerts a small bronchodilator effect in stable COPD **(Evidence A)** and that is associated with modest symptomatic benefits **(Evidence B)**

Fev1 Artırır ,Dispneyi Azaltır ,Sağlık Durumunu İyileştirir,Alevlenmeyi Azaltır

ANTİ İNFLAMATUAR AJANLAR

Anti-Inflammatory Maintenance Therapy

Figure A3.3

Inhaled Corticosteroids

- Regular treatment with ICS increases the risk of pneumonia especially in those with severe disease **(Evidence A)**
- An ICS combined with a LABA is more effective than the individual components in improving lung function and health status and reducing exacerbations in patients with exacerbations and moderate to very severe COPD **(Evidence A)**
- We do not encourage the use of a LABA+ICS combination in COPD. If there is an indication for an ICS the combination LABA+LAMA+ICS has been shown to be superior to LABA+ICS and is therefore the preferred choice
- Triple inhaled therapy of LABA+LAMA+ICS improves lung function, symptoms and health status, and reduces exacerbations, compared to LABA+ICS, LABA+LAMA or LAMA monotherapy **(Evidence A)**. Recent data suggesta beneficial effect of triple inhaled therapy versus fixed-dose LABA+LAMA combinations on mortality in symptomatic COPD patients with a history of frequent and/or severe exacerbations
- If patients with COPD have features of asthma, treatment should always contain an ICS
- Independent of ICS use, there is evidence that a blood eosinophil count < 2% increases the risk of pneumonia **(Evidence C)**
- Combinations can be given as single or multiple inhaler therapy. Single inhaler therapy may be more convenient and effective than multiple inhalers

Antiinflamatuvar tedavilerin etkinliğini değerlendirmede sonlanım noktaları

- **Alevlenme**
- **En az bir alevlenmesi olan hasta sayısı**
- **İlk alevlenmeye kadar geçen süre (time-to-first exacerbation)**

Neden Bu Sonlanımlar?

- **Kronik inflamasyonun klinik etkisi, en belirgin şekilde alevlenmelerde ortaya çıkar!**
- **Antiinflamatuvar ilaç etkinliği, alevlenme yükündeki azalma üzerinden değerlendirilir!**

Biologics

- Dupilumab reduces exacerbations, improves lung function and quality of life, in patients with chronic bronchitis, over 52 weeks **(Evidence A)**
- Mepolizumab reduces exacerbations, in patients with and without chronic bronchitis, over 52 to 104 weeks **(Evidence A)**

Other Anti-Inflammatory Agents

- Statin therapy is not recommended for prevention of exacerbations **(Evidence A)**
- Simvastatin does not prevent exacerbations in COPD patients at increased risk of exacerbations and without indications for statin therapy **(Evidence A)**. However, observational studies suggest that statins may have positive effects on some outcomes in patients with COPD who receive them for cardiovascular and metabolic indications **(Evidence C)**
- Leukotriene modifiers have not been tested adequately in COPD patients

İNHALE KORTİKOSTEROİDLER(İKS)

KOAH'ta İdame Tedaviler

Figure A3.1

Generic Drug Name	Inhaler Type	Nebulizer	Oral/Injectable Delivery	Duration of Action
BETA$_2$-Agonists				
Short-acting (SABA)				
Fenoterol	MDI	✓	tablet, solution	variable
Levalbuterol	MDI	✓		variable
Salbutamol (albuterol)	MDI, DPI	✓	syrup, tablet	variable
Terbutaline	DPI		tablet	variable
Long-acting (LABA)				
Arformoterol		✓		12 hours
Formoterol	DPI	✓		12 hours
Indacaterol	DPI			24 hours
Olodaterol	SMI			24 hours
Salmeterol	MDI, DPI			12 hours
Anticholinergics				
Short-acting (SAMA)				
Ipratropium bromide	MDI	✓		6-8 hours
Oxitropium bromide	MDI	✓		7-9 hours
Long-acting (LAMA)				
Aclidinium bromide	DPI			12 hours
Glycopyrronium bromide	DPI	✓	solution	variable
Tiotropium	DPI, SMI, MDI			24 hours
Umeclidinium	DPI			24 hours
Revefenacin		✓		24 hours
Combination Short-Acting Beta$_2$-Agonist Plus Anticholinergic in One Device (SABA+SAMA)				
Fenoterol/ipratropium	SMI	✓		6-8 hours
Salbutamol/ipratropium	SMI, MDI	✓		variable
Combination Long-Acting Beta$_2$-Agonist Plus Anticholinergic in One Device (LABA+LAMA)				
Formoterol/aclidinium	DPI			12 hours
Formoterol/glycopyrronium	MDI			12 hours
Indacaterol/glycopyrronium	DPI			12-24 hours
Vilanterol/umeclidinium	DPI			24 hours
Olodaterol/tiotropium	SMI			24 hours
Methylxanthines				
Aminophylline			solution, injectable	variable
Theophylline (SR)			tablet, capsule, elixir, solution,	variable
Combination of Long-Acting Beta$_2$-Agonist Plus Corticosteroid in One Device (LABA+ICS)				
Formoterol/beclometasone	MDI, DPI			12 hours
Formoterol/budesonide	MDI, DPI			12 hours
Formoterol/mometasone	MDI			12 hours
Salmeterol/fluticasone propionate	MDI, DPI			12 hours
Vilanterol/fluticasone furoate	DPI			24 hours
Triple Combination in One Device (LABA+LAMA+ICS)				
Fluticasone/umeclidinium/vilanterol	DPI			24 hours
Beclometasone/formoterol/glycopyrronium	MDI, DPI			12 hours
Budesonide/formoterol/glycopyrrolate	MDI			12 hours
Roflumilast			tablet	24 hours
Ensifentrine		✓		12 hours
Mucolytic Agents				
Erdosteine			capsule, suspension	12 hours
Carbocysteine†			capsule, packet, solution, syrup	6-8 hours
N-acetylcysteine†		✓	solution, tablet	2-6 hours
Biologics				
Dupilumab			injectable	2 weeks
Mepolizumab			injectable	4 weeks

*This list is not exhaustive. Not all formulations are available in all countries. In some countries other formulations and dosages may be available. †Dosing regimens are under discussion. MDI = metered dose inhaler; DPI = dry powder inhaler; SMI = soft mist inhaler. Note that glycopyrrolate & glycopyrronium are the same compound.

Meta-Analysis > Cochrane Database Syst Rev. 2012 Sep 12;2012(9):CD006829.

doi: 10.1002/14651858.CD006829.pub2.

Comb
agoni
agoni

Luis Javier

Meta-Analysis > Cochrane Database Syst Rev. 2013 Aug 30;2013(8):CD006826.

doi: 10.1002/14651858.CD006826.pub2.

Combined corticosteroid and long-acting beta(2)-agonist in one inhaler versus inhaled corticosteroids alone for chronic obstructive pulmonary disease

Luis Javier Nannini [1], Phillippa Poole, Stephen J Milan, Annabel Kesterton

ICS+LABA

- **FEV1**
- **Sağlık durumunda iyileşme**
- **Alevlenme azaltma her iki bileşenin tek başına kullanımından daha etkili**
- **Mortaliteye etkisi yok**

Klinik mesaj

ICS etkinliği heterojen

Sigara yükü, eşlik eden bronkodilatör tedavisi,hasta fenotipi tarafından etkilenir.

KOAH'ta ICS seçilmiş hasta gruplarında kullanılmalı

Üçlü Tedavi (LABA+LAMA+ICS)

KOAH'ta İdame Tedaviler

Generic Drug Name	Inhaler Type	Nebulizer	Oral/Injectable Delivery	Duration of Action
BETA$_2$-Agonists				
Short-acting (SABA)				
Fenoterol	MDI	✓	tablet, solution	variable
Levalbuterol	MDI	✓		variable
Salbutamol (albuterol)	MDI, DPI	✓	syrup, tablet	variable
Terbutaline	DPI		tablet	variable
Long-acting (LABA)				
Arformoterol		✓		12 hours
Formoterol	DPI	✓		12 hours
Indacaterol	DPI			24 hours
Olodaterol	SMI			24 hours
Salmeterol	MDI, DPI			12 hours
Anticholinergics				
Short-acting (SAMA)				
Ipratropium bromide	MDI	✓		6-8 hours
Oxitropium bromide	MDI	✓		7-9 hours
Long-acting (LAMA)				
Aclidinium bromide	DPI			12 hours
Glycopyrronium bromide	DPI	✓	solution	variable
Tiotropium	DPI, SMI, MDI			24 hours
Umeclidinium	DPI			24 hours
Revefenacin		✓		24 hours
Combination Short-Acting Beta$_2$-Agonist Plus Anticholinergic in One Device (SABA+SAMA)				
Fenoterol/ipratropium	SMI	✓		6-8 hours
Salbutamol/ipratropium	SMI, MDI	✓		variable
Combination Long-Acting Beta$_2$-Agonist Plus Anticholinergic in One Device (LABA+LAMA)				
Formoterol/aclidinium	DPI			12 hours
Formoterol/glycopyrronium	MDI			12 hours
Indacaterol/glycopyrronium	DPI			12-24 hours
Vilanterol/umeclidinium	DPI			24 hours
Olodaterol/tiotropium	SMI			24 hours
Methylxanthines				
Aminophylline			solution, injectable	variable
Theophylline (SR)			tablet, capsule, elixir, solution, injectable	variable
Combination of Long-Acting Beta$_2$-Agonist Plus Corticosteroid in One Device (LABA+ICS)				
Formoterol/beclometasone	MDI, DPI			12 hours
Formoterol/budesonide	MDI, DPI			12 hours
Formoterol/mometasone	MDI			12 hours
Salmeterol/fluticasone propionate	MDI, DPI			12 hours
Triple Combination in One Device (LABA+LAMA+ICS)				
Fluticasone/umeclidinium/vilanterol	DPI			24 hours
Beclometasone/formoterol/glycopyrronium	MDI, DPI			12 hours
Budesonide/formoterol/glycopyrrolate	MDI			12 hours
Phosphodiesterase-3 and/or -4 Inhibitors				
Ensifentrine		✓		12 hours
Mucolytic Agents				
Erdosteine			capsule, suspension	12 hours
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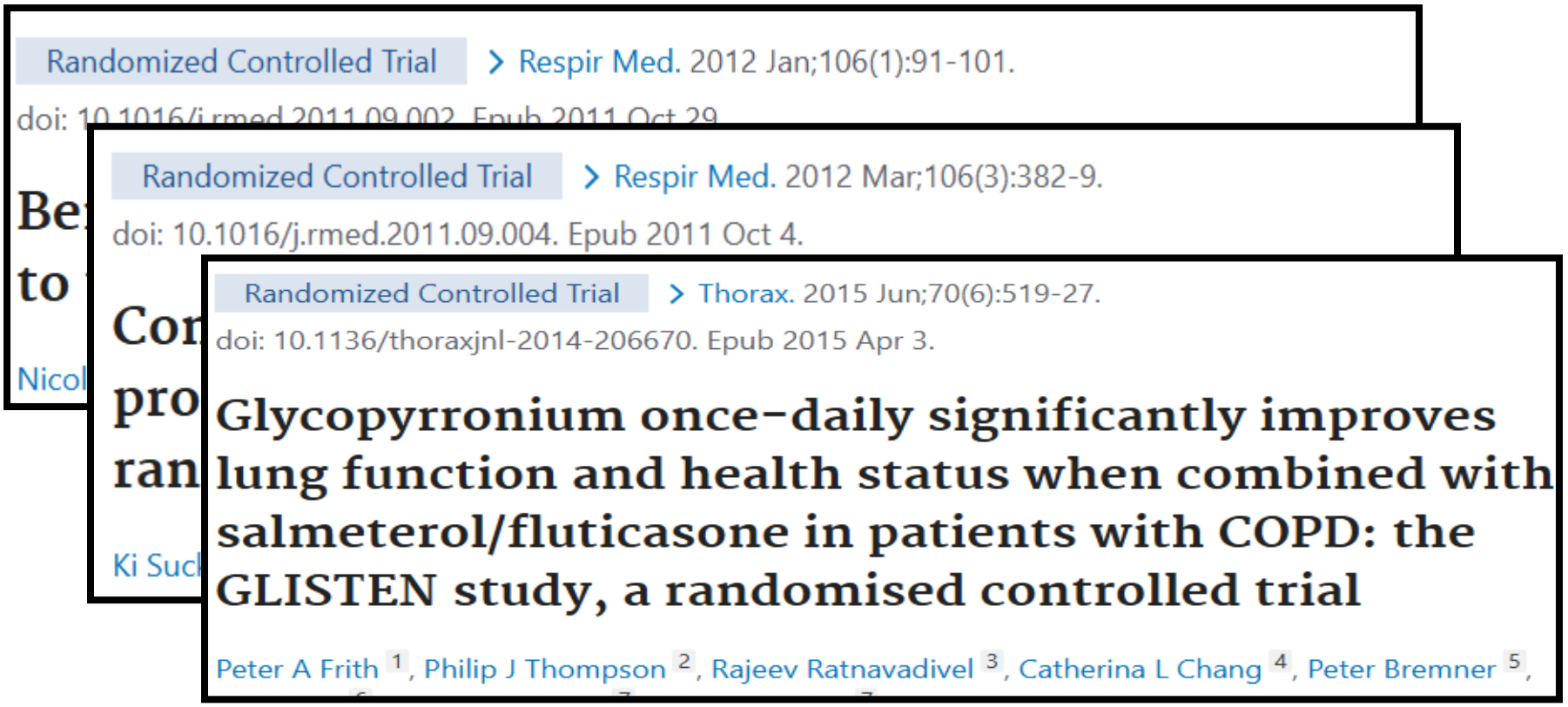
Oral glukokortikoidler



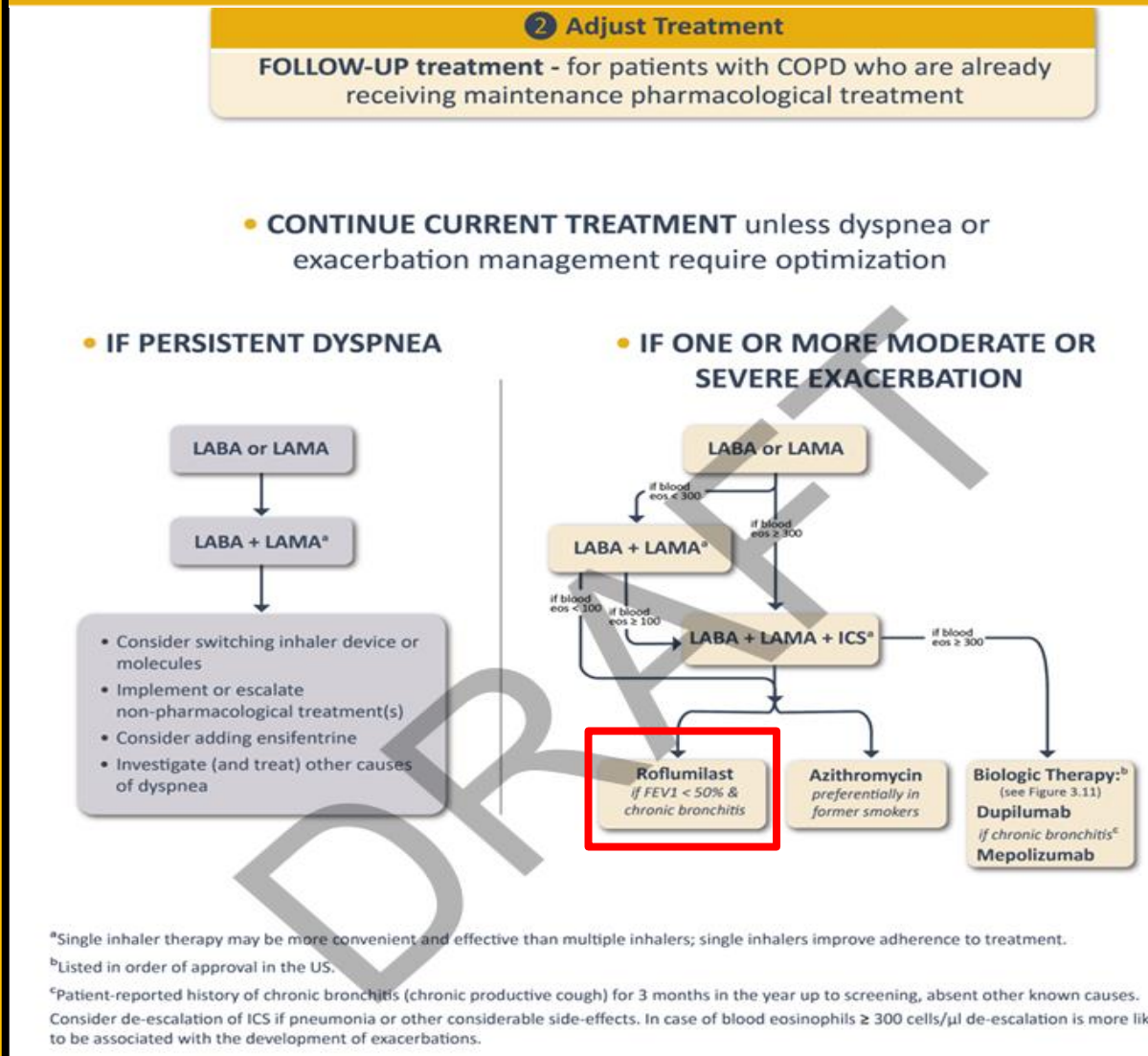
Oral glukokortikoidler

Steroid miyopatisi ,kas güçsüzlüğü, fonksiyonel kapasitede azalma,solunum yetmezliği

Fosfodiesteraz 4 inhibitörü: Roflumilast

Follow-up Pharmacological Treatment

Figure 3.9



[a]Single inhaler therapy may be more convenient and effective than multiple inhalers; single inhalers improve adherence to treatment.

[b]Listed in order of approval in the US.

[c]Patient-reported history of chronic bronchitis (chronic productive cough) for 3 months in the year up to screening, absent other known causes. Consider de-escalation of ICS if pneumonia or other considerable side-effects. In case of blood eosinophils ≥ 300 cells/µl de-escalation is more likely to be associated with the development of exacerbations.

Anti-Inflammatory Maintenance Therapy

Figure A3.3

Inhaled Corticosteroids	• Regular treatment with ICS increases the risk of pneumonia especially in those with severe disease **(Evidence A)** • An ICS combined with a LABA is more effective than the individual components in improving lung function and health status and reducing exacerbations in patients with exacerbations and moderate to very severe COPD **(Evidence A)** • We do not encourage the use of a LABA+ICS combination in COPD. If there is an indication for an ICS the combination LABA+LAMA+ICS has been shown to be superior to LABA+ICS and is therefore the preferred choice • Triple inhaled therapy of LABA+LAMA+ICS improves lung function, symptoms and health status, and reduces exacerbations, compared to LABA+ICS, LABA+LAMA or LAMA monotherapy **(Evidence A)**. Recent data suggesta beneficial effect of triple inhaled therapy versus fixed-dose LABA+LAMA combinations on mortality in symptomatic COPD patients with a history of frequent and/or severe exacerbations • If patients with COPD have features of asthma, treatment should always contain an ICS • Independent of ICS use, there is evidence that a blood eosinophil count < 2% increases the risk of pneumonia **(Evidence C)** • Combinations can be given as single or multiple inhaler therapy. Single inhaler therapy may be more convenient and effective than multiple inhalers
Oral Glucocorticoids	• Long-term use of oral glucocorticoids has numerous side effects **(Evidence A)** with no evidence of benefits **(Evidence C)**
PDE Inhibitors	• In patients with chronic bronchitis, severe to very severe COPD and a history of exacerbations: • Roflumilast improves lung function and reduces moderate and severe exacerbations **(Evidence A)** • Ensifentrine improves lung function **(Evidence A)** but an effect on exacerbations has not been evaluated in patients at increased exacerbation risk
Antibiotics	• Long-term azithromycin and erythromycin therapy reduces exacerbations over one year **(Evidence A)** • Preferentially, but not only in former smokers with exacerbations despite appropriate therapy, azithromycin can be considered **(Evidence B)** • Treatment with azithromycin is associated with an increased incidence of bacterial resistance **(Evidence A)** and hearing test impairments **(Evidence B)**
Mucoregulators & Antioxidant Agents	• Regular treatment with mucolytics such as erdosteine, carbocysteine and N-acetylcysteine reduces the risk of exacerbations in select populations **(Evidence B)** • Antioxidant mucolytics are recommended only in selected patients **(Evidence A)**

Biologics	• In patients with COPD with blood eosinophils ≥ 300 cells/µL (**see Figure 3.11**) who are uncontrolled on triple therapy:
	  • Dupilumab reduces exacerbations, improves lung function and quality of life, in patients with chronic bronchitis, over 52 weeks **(Evidence A)**
	  • Mepolizumab reduces exacerbations, in patients with and without chronic bronchitis, over 52 to 104 weeks **(Evidence A)**

Other Anti-Inflammatory Agents	• Statin therapy is not recommended for prevention of exacerbations (**Evidence A**) • Simvastatin does not prevent exacerbations in COPD patients at increased risk of exacerbations and without indications for statin therapy **(Evidence A)**. However, observational studies suggest that statins may have positive effects on some outcomes in patients with COPD who receive them for cardiovascular and metabolic indications **(Evidence C)** • Leukotriene modifiers have not been tested adequately in COPD patients

Teşekkür ederim...