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REVIEW

Practical considerations when prescribing a long-acting muscarinic antagonist for patients with COPD

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Abstract: COPD is characterized by persistent airflow limitation, progressive breathlessness, cough, and sputum production. Long-acting muscarinic antagonists (LAMAs) are one of the recommended first-choice therapeutic options for patients with COPD, and several new agents have been developed in recent years. A literature search identified 14 published randomized, placebo-controlled studies of the efficacy and safety of LAMAs in patients with COPD, with improvements seen in lung function, exacerbations, breathlessness, and health status. A greater weight of evidence currently exists for glycopyrronium (GLY) and tiotropium than for umeclidinium and aclidinium, especially in terms of exacerbation reductions. To date, there have been few head-to-head clinical studies of the different LAMAs. Available data indicate that GLY and aclidinium have similar efficacy to tiotropium in terms of improving lung function, dyspnea, exacerbations, and health status. Overall, evidence demonstrates that currently available LAMAs provide effective and generally well-tolerated therapy for patients with COPD. Delivery devices for the different LAMAs vary, which may affect individual patient's adherence to and preference for treatment. Subtle differences between individual therapeutic options may be important to individual patients and the final treatment choice should involve physician's and patient's experiences and preferences.

Keywords: COPD, long-acting muscarinic antagonist, efficacy, safety, inhaler, adherence

Introduction

COPD is a common, preventable and treatable disease characterized by persistent respiratory symptoms and airflow limitation.[1] Damage caused by a combination of small airway disease (obstructive bronchiolitis) and parenchymal destruction (emphysema) results in the characteristic symptoms of COPD: progressive breathlessness on exertion and persistent airflow limitation.

Airflow limitation may be improved using bronchodilators, which alter airway smooth muscle tone, thereby reducing airway resistance and static and dynamic hyperinflation.[1–3] Both classes of long-acting bronchodilator (long-acting muscarinic antagonists [LAMAs; also known as anticholinergics] and long-acting β_2-agonists [LABAs]) improve lung function, symptoms, health status, exercise tolerance, and exacerbations in COPD patients.[1] LABAs may be more effective than LAMAs at reducing symptoms (although results are conflicting),[4,5] while LAMAs may be superior to LABAs for exacerbation prevention.[6,7] The complementary mechanisms of action of LABAs and LAMAs elicit additive effects on lung function and provide rationale for combining the two classes.[1] In this review, we focus on the available evidence for the efficacy and safety of LAMAs in the management of COPD.

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In 2002, tiotropium 18 µg once daily (qd) was the first LAMA to be approved for the maintenance treatment of patients with COPD,[8,9] followed by glycopyrronium (GLY) 50 µg qd, which was approved in Europe in 2012.[10] More recently, umeclidinium 65 µg qd[11] and aclidinium 400 µg twice daily (bid) were also approved.[9]

The Global initiative for Obstructive Lung Disease (GOLD) 2018 strategy document contains substantial revisions to the committee's recommendations for diagnosis, classification, and treatment of patients with COPD, including their recommendations for LAMA use.[1] According to GOLD, LAMA monotherapy may be an appropriate treatment for all patients with COPD, irrespective of the GOLD group to which their disease is assigned. Moreover, a LAMA is recommended as part of a dual or triple combination for those patients with persistent or severe breathlessness or persistent exacerbations, ie, GOLD Groups B–D.

Accordingly, LAMAs may be used as first-choice therapy for patients with few symptoms and no exacerbation history (GOLD Group A).[1] In this patient group, GOLD recommends either a short-acting bronchodilator or long-acting bronchodilator of either class.[1] Initial treatment with LAMA or LABA monotherapy is recommended for symptomatic patients at low risk of exacerbation (GOLD Group B), escalating to dual bronchodilation if breathlessness persists. GOLD does not recommend one class of bronchodilator over another for Group B patients and states that choice should depend on individual perception of symptom relief.[1]

GOLD also recommends initial treatment with LAMA monotherapy in patients with an exacerbation history but few symptoms (GOLD Group C).[1] In both POET (Prevention of Exacerbations with Tiotropium) and INVIGORATE (Indacaterol: Providing Opportunity to Re-engage Patients with Life), the LAMA tiotropium demonstrated a greater effect on annual exacerbation rate than a LABA (salmeterol and indacaterol [IND], respectively) in patients with severe COPD.[6,7] If patients experience further exacerbations on LAMA monotherapy, GOLD recommends escalating treatment to LABA/LAMA (preferred choice) or inhaled corticosteroid (ICS)/LABA (alternative choice).[1] Group C patients are not commonly studied in clinical trials, and there is little validated information regarding the treatment of these patients.

The Spanish Guidelines for COPD (GesEPOC) also suggest that patients who require a long-acting bronchodilator as monotherapy should use a LAMA in the first instance, based on greater reductions in exacerbations with tiotropium compared with LABAs.[12–14] In symptomatic patients, the GesEPOC guidelines recommend a combination of LABA/LAMA.[15]

LAMAs have a clear role in treatment recommendations.[1] However, the rapid arrival of new medications for the management of COPD, each with a distinct delivery inhaler and supporting evidence, has created considerable prescriber confusion. Here, we compare clinical evidence for currently available LAMAs to further clarify appropriate treatment selection and advise practicing physicians on the management of patients with COPD.

Methods

The PubMed database was searched ([aclidinium OR GLY OR tiotropium OR umeclidinium] AND COPD AND placebo AND randomized) to identify English language publications of studies of currently available LAMAs as the active treatment in patients with COPD. Results were filtered to identify primary publications of randomized, double-blind, placebo-controlled studies of ≥6 months' duration using approved doses of the four available LAMAs. Information was retrieved from the corresponding summary of product characteristics (SmPC) and from regulatory documentation available at the European Medicines Agency (EMA).[8–11,16,17]

Results

The literature search identified 366 publications, of which 14 were primary publications of double-blind, randomized, placebo-controlled studies of ≥6 months duration for the four LAMAs (Table 1).[18–31] Of the 14 studies, six studies evaluated tiotropium 18 µg qd (HandiHaler®), two studies evaluated tiotropium 5 µg qd (Respimat®), two studies evaluated GLY 50 µg qd, one study evaluated umeclidinium 62.5 µg qd, and three studies evaluated aclidinium 400 µg bid. Aclidinium has also been evaluated in a 52-week extension to a 12-week randomized, double-blind, placebo-controlled trial (during the extension, patients received aclidinium 200 or 400 µg qd, with no placebo arm).[32] In the USA, GLY 12.5 µg has been developed for twice-daily use;[33,34] however, this is outside the scope of this review.

The outcomes below were included in the majority of studies and provided a basis for comparing efficacy between LAMAs.

Lung function

Forced expiratory volume in 1 second (FEV_1) is a validated and important measure of lung function in COPD. Not only is FEV_1 a predictor of all-cause mortality[1,35] but also is correlated to COPD symptoms, exacerbations, and overall health care resource use and costs.[36]

Trough FEV_1 (measured 12 hours after the preceding dose of a twice-daily treatment or 24 hours after a once-daily

Table 1 Double-blind, randomized, placebo-controlled studies of LAMA therapy with durations of at least 6 months

Study	Duration	N	Baseline FEV_1 % predicted[a]	Treatments	Concomitant maintenance treatment for COPD
Tiotropium (via HandiHaler® device)					
Casaburi et al (2002)[18]	1 year ×2[b]	921	39[c]	Tiotropium 18 μg qd Placebo (3:2)	Theophylline; ICS/OCS
Donohue et al (2002)[19]	6 months	623	40[c]	Tiotropium 18 μg qd Salmeterol 50 μg bid Placebo (1:1:1)	ICS/OCS
Niewoehner et al (2005)[20]	6 months	1,829	36 (≤60 predicted)[c]	Tiotropium 18 μg qd Placebo (1:1)	Study treatment given in addition to LABA or LABA/ICS
Chan et al (2007)[21]	48 weeks	913	39 (≤65 predicted)[c]	Tiotropium 18 μg qd Placebo (2:1)	Study treatment given in addition to LABA or LABA/ICS
Tashkin et al (2008) (UPLIFT)[22]	4 years	5,993	48 (GOLD II–IV)	Tiotropium 18 μg qd Placebo (1:1)	Study treatment given in addition to LABA or LABA/ICS
Troosters et al (2014)[23]	24 weeks	457	66 (GOLD II)	Tiotropium 18 μg qd Placebo (1:1)	OCS (up to 2 weeks for acute exacerbations)
Tiotropium (via Respimat® device)					
Bateman et al (2010)[24]	1 year ×2[b]	1,990	45–47	Tiotropium 5 μg qd Tiotropium 10 μg qd Placebo (1:1:1)	ICS/OCS; theophylline
Bateman et al (2010)[25]	1 year	3,991	45	Tiotropium 5 μg qd Placebo (1:1)	Study treatment given in addition to LABA or LABA/ICS
Glycopyrronium					
D'Urzo et al (2011) (GLOW1)[26]	26 weeks	822	54–55 (GOLD II–IV)	Glycopyrronium 50 μg qd Placebo (2:1)	ICS at stable dose; OCS and/or SABA for exacerbations
Kerwin et al (2012) (GLOW2)[27]	52 weeks	1,066	56 (GOLD II–IV)	Glycopyrronium 50 μg qd Tiotropium 18 μg qd OL Placebo (2:1:1)	ICS at stable dose; OCS and/or SABA for exacerbations
Umeclidinium					
Donohue et al (2013)[28]	24 weeks	1,532	47–48 (GOLD II–IV)	Umeclidinium/vilanterol 62.5/25 μg qd Umeclidinium 62.5 μg qd Vilanterol 25 μg qd Placebo (3:3:3:2)	ICS at stable dose
Aclidinium					
Jones et al (2012) (ATTAIN)[29]	24 weeks	828	57 (GOLD II/III)	Aclidinium 200 μg bid Aclidinium 400 μg bid Placebo (1:1:1)	ICS; theophylline; OCS; oxygen therapy
Singh et al (2014) (ACLIFORM)[30]	24 weeks	1,729	54 (GOLD II/III)	Aclidinium/formoterol 400/12 μg bid Aclidinium/formoterol 400/6 μg bid Aclidinium 400 μg Formoterol 12 μg bid Placebo (2:2:2:2:1)	ICS; theophylline; OCS; oxygen therapy
D'Urzo et al (2014) (AUGMENT)[31]	24 weeks	1,692	53–55	Aclidinium/formoterol 400/12 μg bid Aclidinium/formoterol 400/6 μg bid Aclidinium 400 μg bid Formoterol 12 μg bid Placebo (1:1:1:1:1)	Stable doses of theophylline, ICS, or systemic corticosteroids permitted

Notes: In all studies, use of other anticholinergics/muscarinic antagonists was not permitted. [a]Postbronchodilator FEV_1, unless otherwise stated. [b]Two 1-year studies were evaluated. [c]Reference does not specify if this is pre- or postbronchodilator FEV_1.

Abbreviations: bid, twice daily; FEV_1, forced expiratory volume in 1 second; GOLD, Global initiative for chronic Obstructive Lung Disease; ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic antagonist; OCS, oral corticosteroids; OL, open label; qd, once daily; SABA, short-acting β_2-agonist.

treatment) provides a valid and clinically relevant measure of the activity of a bronchodilator across a 12 or 24 hours' period. A 100 mL change in FEV_1 has been reported as the minimum clinically important difference (MCID) at which patients can perceive a difference in lung function.[37] Trough FEV_1 was evaluated in all 14 of the studies identified in the literature search (Table 2).[18–31] LAMA monotherapy increased trough FEV_1 by ~100 mL compared with placebo.

Table 2 Lung function in patients receiving LAMA therapy, compared with placebo, in double-blind, randomized, placebo-controlled studies ≥6 months in duration

Study	FEV_1 at baseline (mL)		Trough FEV_1 (mL)	
	Treatment	Placebo	Δ vs placebo (at time point)	*P*-value
Tiotropium 18 µg qd (via HandiHaler® device)				
Casaburi et al (2002)[18]	1,000	1,040	120–150[a] (49 weeks)	<0.01
Donohue et al (2002)[19]	1,110	1,060	137 (24 weeks)	<0.0001
Niewoehner et al (2005)[20]	1,040	1,040	100 (6 months)	<0.001
Chan et al (2007)[21]	970	960	100 (48 weeks)[a]	<0.0001
Tashkin et al (2008) (UPLIFT)[22]	1,330	1,332	87–103 (over study period to 48 months)[a]	<0.001
Troosters et al (2014)[23]	1,950	1,900	140 (week 24)	<0.001
Kerwin et al (2012) (GLOW2)[27]	1,500	1,500	83 (week 12) 84 (week 26) 89 (week 52)	<0.001
Tiotropium 5 µg qd (via Respimat® device)				
Bateman et al (2010)[24]	1,066	1,058	127 (week 48)[a]	<0.0001
Bateman et al (2010)[25]	1,109	1,101	102 (week 48)[a]	<0.0001
Glycopyrronium 50 µg qd				
D'Urzo et al (2011) (GLOW1)[26]	1,490	1,450	105 (week 12)[a] 113 (week 26)	<0.001
Kerwin et al (2012) (GLOW2)[27]	1,500	1,500	97 (week 12)[a] 134 (week 26) 108 (week 52)	<0.001
Umeclidinium 62.5 µg qd				
Donohue et al (2013)[28]	NR	NR	115 (day 169)[a]	<0.001
Aclidinium 400 µg bid				
Jones et al (2012) (ATTAIN)[29]	1,510	1,500	128 (week 24)[a]	<0.0001
Singh et al (2014) (ACLIFORM)[30]	1,400	1,420	117 (week 24)	<0.001
D'Urzo et al (2014) (AUGMENT)[31]	1,340	1,350	~101 (week 24)[b]	<0.0001

Notes: Results for FEV_1 are expressed as active treatment minus placebo values. All differences vs placebo are statistically significant unless otherwise indicated. [a]Primary endpoint. [b]Estimated from figure.
Abbreviations: bid, twice daily; FEV_1, forced expiratory volume in 1 second; LAMA, long-acting muscarinic antagonist; NR, not reported; qd, once daily.

Postbronchodilator FEV_1 (based on spirometry measurements, commonly 30–45 minutes postadministration of a short-acting bronchodilator) is used for assessing the severity of airflow limitation in patients with COPD.[1,22,38] In the UPLIFT (Understanding Potential Long-Term Impacts on Function with Tiotropium) study, the rate of decline in postbronchodilator FEV_1 was 40±3 mL in the tiotropium group and 47±3 in the placebo group (P=0.046), suggesting an improvement in airflow limitation in the LAMA group compared with placebo.[22]

Measures of hyperinflation can also provide evidence for the efficacy of bronchodilators.[39,40] Increases in inspiratory capacity (IC) may be a more sensitive marker for improvements in hyperinflation than FEV_1 in patients with moderate–severe COPD.[39,40] One study found that tiotropium achieved sustained reductions in lung hyperinflation, measured by lung volume and IC, at rest and during exercise.[41] In addition, use of tiotropium resulted in increases in IC, improving the effects of breathlessness and increasing exercise endurance in stable patients with COPD.[41] Furthermore, improvements in exercise tolerance accompanied by sustained reductions in lung hyperinflation signified by improvements in IC were seen in moderate-to-severe COPD patients treated with GLY and aclidinium.[42,43]

Exacerbations

GOLD 2018 defines an exacerbation as "an acute worsening of respiratory symptoms that results in additional therapy".[1] In clinical trials, the severity of an exacerbation is often determined by the level of management required, eg, patient self-management (mild), treatment with antibiotics/oral corticosteroids (moderate), or emergency room attendance/hospitalization (severe).[44] The rate of mild exacerbations recorded may vary between studies due to the method used to record patient symptoms, such as patient diaries[45] and the EXAcerbations of Chronic pulmonary disease Tool for Patient-Reported Outcomes (EXACT-PRO).[14] Furthermore, the rate of severe exacerbations as defined by

hospital/emergency room admission may reflect variations in disease management seen within health care systems; for example, a 10-fold variation in hospital admission rates for COPD has been reported between European countries.[45,46]

Accurate assessment of differences in exacerbations requires appropriately powered studies of suitably long duration (≥1 year); often, data with newer LAMAs are from shorter studies powered for efficacy endpoints such as trough FEV_1.[19–21,23,26,28–31] Endpoints used to assess drug effects may differ between studies; exacerbation rates[19,21,23,29,30] and time-to-first exacerbation[18,20,22,24–28] are commonly used to assess differences between treatment arms. Differential dropout rates between treatment arms can result in a loss of statistical power to detect differences in event rates; however, analysis by "time-to-first event" avoids this problem and provides a truer indication of drug effect on exacerbations.

Exacerbation rates were evaluated in 11 of the 14 studies identified (Table 3).[18–31] Although the overall rate

Table 3 Effect on exacerbations in patients receiving LAMA therapy, compared with placebo, in double-blind, randomized, placebo-controlled studies ≥6 months in duration

Study	Annual exacerbation rate (treatment vs placebo)			% patients with ≥1 exacerbation			Risk reduction in time to first exacerbation (*P*-value)	Exacerbation type
	Placebo	Treatment	Treatment vs placebo (*P*-value)	Placebo	Treatment	Treatment vs placebo (*P*-value)		
Tiotropium (via HandiHaler® device)								
Casaburi et al (2002)[18]	0.95	0.76	20% reduction (0.045)	42	36	14% reduction (<0.05)	NR (0.011)	All
Donohue et al (2002)[19]	NR	NR	NR	NR	NR	NR	NR	NR
Niewoehner et al (2005)[20]	1.05	0.85	NR (0.031)	32	28	OR =0.81[a] (0.037)	17% (0.028)	Moderate or severe
Chan et al (2007)[21]	0.92	0.88	NR (NS)	41	44	NR (NS)	NR	Moderate
Tashkin et al (2008) (UPLIFT)[22]	0.85	0.73	Relative risk =0.86 (<0.001)	68	67	NR (NS)	14% (<0.001)	Moderate
Troosters et al (2014)[23]	NR	NR	NR	NR	NR	NR	NR	
Kerwin et al (2012) (GLOW2)[27]	NR	NR	NR (NS)	NR	NR	RR =0.80 (NS)	39% (0.001)	Moderate or severe
Tiotropium (via Respimat® device)								
Bateman et al (2010)[b,24]	1.91	0.93	NR (NS)	44	37	OR =0.75 (<0.01)	NR (<0.0001)	Moderate
Bateman et al (2010)[25]	0.87	0.69	Relative rate =0.79 (<0.0001)	43	35	HR =0.69 (<0.0001)	31%[a] (<0.0001)	Mild or moderate
Glycopyrronium 50 μg qd								
D'Urzo et al (2011) (GLOW1)[26]	0.59	0.43	RR =0.72 (NS)	24	18	NR	31% (0.023)	Moderate or severe
	NR	NR	NR	NR	NR	NR	65% (0.022)	Severe
Kerwin et al (2012) (GLOW2)[27]	NR	NR	NR	0.80	0.54	RR =0.66 (0.003)	34% (0.001)	Moderate or severe
Umeclidinium 62.5 μg qd								
Donohue et al (2013)[28]	NR	NR	NR	13	NR, 7%–9% in active groups	NR (NR)	~40% (<0.05)	Moderate or severe
Aclidinium 400 μg bid								
Jones et al (2012) (ATTAIN)[29]	0.47	0.34	RR =0.72 (NS)	NR	NR	NR	NR	Moderate or severe
	0.60	0.40	RR =0.67 (<0.05)	NR	NR	NR	NR	All
Singh et al (2014) (ACLIFORM)[30]	0.36	0.29	NR (NS)	NR	NR	NR	NR	All (HCRU)
D'Urzo et al (2014) (AUGMENT)[31]	NR	NR	NR	NR	NR	NR	NR	

Notes: Mild exacerbation defined as increase in symptoms for ≥2 days resulting in an increased use of short-acting bronchodilators and/or ICS. Moderate exacerbation defined as new/increased cough, sputum, sputum purulence, dyspnea, wheeze, or chest discomfort for ≥3 days requiring antibiotics and/or systemic steroids. Severe exacerbations defined as exacerbations leading to hospitalization. HCRU, Healthcare Resource Utilization (defined as an increase of COPD symptoms during ≥2 consecutive days that require a change in COPD treatment). [a]Primary endpoint. [b]Pooled analysis of two studies (difference in time to first exacerbation was not significant in one of the two studies).

Abbreviations: bid, twice daily; HR, hazard ratio; ICS, inhaled corticosteroid; LAMA, long-acting muscarinic antagonist; NR, not reported; NS, not statistically significant; OR, odds ratio; qd, once daily; RR, rate ratio.

of exacerbations was low (generally <1 per year in placebo recipients), statistically significant reductions were reported. In three of the four studies in which exacerbations were assessed, tiotropium (HandiHaler®) significantly reduced the rate of moderate-to-severe exacerbations and all (mild, moderate, or severe) exacerbations compared with placebo,[18,20,22] while in the remaining study, no significant reduction in moderate-to-severe exacerbations was observed.[21] Tiotropium (Respimat®) significantly reduced the rate of moderate-to-severe exacerbations compared with placebo in two studies.[24,25]

Similarly, GLY significantly decreased the risk of first moderate-to-severe exacerbation compared with placebo in both GLOW1 (Glycopyrronium Bromide in COPD AirWays) and GLOW2 studies and significantly reduced the rate of moderate-to-severe exacerbations in GLOW2.[26,27] Umeclidinium also significantly reduced the risk of time-to-first moderate or severe exacerbation compared with placebo, although the study did not report on exacerbation rate.[28] Aclidinium significantly reduced all exacerbations vs placebo in ATTAIN (Aclidinium to Treat Airway Obstruction in COPD Patients) but had no significant effect on the frequency of moderate-to-severe exacerbations in ATTAIN or ACLIFORM.[29,30] Finally, aclidinium significantly reduced the rate of moderate-to-severe exacerbations compared with placebo in a pooled analysis of data from ATTAIN and Aclidinium in Chronic Obstructive Respiratory Disease (ACCORD).[47] Overall, evidence indicates that LAMAs are effective at reducing the risk of exacerbations in COPD patients.

Dyspnea

Dyspnea is the fundamental symptom of COPD.[1] Tools to measure dyspnea include the transition dyspnea index (TDI), which is widely used in clinical trials.[48,49] TDI measures changes from a baseline state of dyspnea severity in three categories (functional impairment, magnitude of task, and magnitude of effort) and sums to give a score of 0–12 points, with a lower score indicating a greater deterioration in dyspnea severity.[49] A ≥1-unit change in TDI score is defined as the MCID.[50]

TDI was measured in nine of the 14 studies (Table 4).[18–31] LAMA significantly reduced TDI, with more patients responding to therapy and attaining the MCID vs placebo.[18,19,24,26–31] These findings indicate that LAMAs are effective at reducing breathlessness that patients are likely to perceive as beneficial.

Health status

St George's Respiratory Questionnaire (SGRQ) is one of the most widely used tools to assess health status in patients with respiratory disease. SGRQ measures the following three components: frequency and severity of respiratory symptoms, activities that cause dyspnea and are limited by dyspnea, and an "impacts" section, covering aspects of employment, loss of control, expectations, and disturbance to daily life.[51] Total scores range between 0 and 100 units; higher scores indicate a greater impact on health status. A change in the score of ≥4, compared with either baseline (when assessing an individual's response to treatment) or placebo (for treatment efficacy evaluation in clinical trials), is established as the MCID.[51–53]

Health status was assessed using SGRQ in 11 of the 14 studies (Table 3).[18–31] Compared with placebo, treatment with tiotropium or GLY resulted in numerical improvements in health status in eight studies; however, differences in SGRQ total score were between −2.7 and −3.5 units and were less than the MCID.[18,19,21,22,24–27] Umeclidinium significantly improved SGRQ total score from baseline and exceeded the MCID compared with placebo (−4.69).[28] Aclidinium significantly improved health status from baseline by a similar amount vs placebo in both ATTAIN and AUGMENT (−4.6 and −4.2, respectively);[29,31] however, no significant difference was observed in ACLIFORM.[30] Authors of ACLIFORM attributed a high placebo effect to the lack of significance seen despite the large change from baseline in SGRQ score (−5.8 to −8.3 units with regimens containing aclidinium vs −6.5 units with placebo).[30] In general, LAMAs showed an improvement in SGRQ total score compared with placebo, with several studies demonstrating clinically relevant differences.

Safety

The frequency of adverse events (AEs) was similar between LAMA and placebo in seven of the 14 studies,[18,20,24–26,29,30] with few observed differences in the incidence of individual AEs (excluding typical anticholinergic AEs). Compared with placebo, a lower frequency of serious AEs occurred with GLY (12.6 vs 16.0%),[27] whereas a higher frequency was observed with tiotropium (HandiHaler®) in two studies (18.4 vs 14.1% and 51.6 vs 50.2%),[21,22] umeclidinium in one study (6.0 vs 3.0%),[28] and aclidinium in one study (5.0 vs 3.6%).[31] There were no observed differences in mortality between LAMA and placebo.

Anticholinergic AEs include dry mouth, constipation, dysuria, and urinary tract infections.[1] While few studies

Table 4 Dyspnea, health status, and rescue medication use in patients receiving LAMA therapy, compared with placebo, in double-blind, randomized, placebo-controlled studies ≥6 months in duration

Study	Treatments	TDI focal score		Health status (SGRQ)		Rescue medication use (treatment vs placebo)
		Δ vs placebo	Responders (%) (treatment vs placebo)	Δ vs placebo	Responders (%) (treatment vs placebo)	
Tiotropium (via HandiHaler® device)						
Casaburi et al (2002)[18]	Tiotropium 18 µg qd	0.8–1.1 *P*<0.001	42–47 vs 29–34 *P*<0.001	NR *P*<0.05	49 vs 30 Significant but *P*-value not given	3.2 vs 4.1 doses/day *P*<0.01
Donohue et al (2002)[19]	Tiotropium 18 µg qd	1.02 *P*=0.01	42 vs 26 *P*<0.01	–2.71 *P*<0.05	51 vs 42 *P*<0.05	–1.45 puffs/day vs placebo *P*<0.0001
Niewoehner et al (2005)[20]	Tiotropium 18 µg qd	NR	NR	NR	NR	NR
Chan et al (2007)[21]	Tiotropium 18 µg qd	NR	NR	–2.8 *P*<0.01	53 vs 44 NS	~6 fewer puffs/week vs placebo *P*<0.01
Tashkin et al (2008) (UPLIFT)[22]	Tiotropium 18 µg qd	NR	NR	–2.7 *P*<0.001	45–49 vs 36–41 *P*<0.001	NR
Troosters et al (2014)[23]	Tiotropium 18 µg qd	NR	NR	NR	NR	NR
Kerwin et al (2012) (GLOW2)[27]	Tiotropium 18 µg qd OL					
	Week 26	0.94 *P*=0.002	53.4 vs 44.2 *P*=0.032	–2.52 *P*<0.05	NR	NR
	Week 52	0.66 *P*=0.037	NR	–2.84 *P*=0.014	59 vs 51 NS	–0.63 puffs/day *P*<0.01
Tiotropium (via Respimat® device)						
Bateman et al (2010)[24]	Tiotropium 5 µg qd	1.05 *P*<0.0001	56 vs 44 *P*<0.0001	–3.5 *P*<0.0001	51 vs 41 *P*<0.05	–0.6 occasions/day *P*<0.0001
Bateman et al (2010)[25]	Tiotropium 5 µg qd	NR	NR	–2.9 *P*<0.0001	50 vs 41 *P*<0.0001	NR
Glycopyrronium						
D'Urzo et al (2011) (GLOW1)[26]	Glycopyrronium 50 µg qd	1.04 *P*<0.001	61 vs 48 *P*=0.001	–2.8 *P*=0.004	57 vs 46 *P*=0.006	–0.46 puffs/day *P*=0.005
Kerwin et al (2012) (GLOW2)[27]	Glycopyrronium 50 µg qd					
	Week 26	0.81 *P*=0.002	55 vs 44 *P*=0.01	–3.38 *P*<0.001	NR	NR
	Week 52	0.57 *P*=0.038	NR	–3.32 *P*<0.001	54 vs 51 NS	–0.37 puffs/day *P*<0.05
Umeclidinium						
Donohue et al (2013)[28]	Umeclidinium 62.5 µg qd	1.0 *P*≤0.001	53 vs 41 *P*≤0.01	–4.69 *P*≤0.001	44 vs 34 *P*≤0.01	–0.3 puffs/day NS
Aclidinium						
Jones et al (2012) (ATTAIN)[29]	Aclidinium 400 µg bid	1.0 *P*<0.001	57 vs 46 *P*<0.01	–4.6 *P*<0.0001	57 vs 41 *P*<0.001	–0.95 puffs/day *P*<0.0001
Singh et al (2014) (ACLIFORM)[30]	Aclidinium 400 µg bid	0.9 *P*<0.01	57 vs 46 *P*<0.05	0.71 NS	NR	NR
D'Urzo et al (2014) (AUGMENT)[31]	Aclidinium 400 µg bid	0.98[a] *P*≤0.001	55 vs 37 *P*≤0.001	–4.23[a] *P*≤0.001	55 vs 39 *P*≤0.001	–0.68 from baseline with aclidinium (placebo NR) *P*<0.0001

Notes: All comparisons are vs placebo. Responder analyses represent percentages of patients with TDI score ≥1 or SGRQ improvement ≥4 points. [a]Values are estimated from figures in the associated reference.

Abbreviations: bid, twice daily; LAMA, long-acting muscarinic antagonist; NR, not reported; NS, not statistically significant; OL, open label; qd, once daily; SAL, salmeterol; SGRQ, St George's Respiratory Questionnaire; TDI, transition dyspnea index.

reported anticholinergic AEs, the incidence of dry mouth was reported in some studies, with rates ranging from 1.3 to 16% with tiotropium (HandiHaler®), 3.1 to 7.2% with tiotropium (Respimat®), and 0.6 to 0.7% with aclidinium (Table 5).[18–31] In a 52-week extension to the 12-week ACCORD trial, the incidence of dry mouth was similar between patients receiving aclidinium 200 and 400 µg.[32] No specific data were provided for studies of GLY or umeclidinium. Details provided

Table 5 AEs in patients receiving LAMA therapy, compared with placebo, in double-blind, randomized, placebo-controlled studies ≥6 months in duration

Study	Treatments	Typical anticholinergic AEs (% patients)		
		Dry mouth	Constipation	UTI
Tiotropium (via HandiHaler® device)				
Casaburi et al (2002)[18]	Tiotropium 18 μg qd/placebo	16/2.7	NR	NR
Donohue et al (2002)[19]	Tiotropium 18 μg qd/placebo	10/NR	NR	NR
Niewoehner et al (2005)[20]	Tiotropium 18 μg qd/placebo	NR	NR	NR
Chan et al (2007)[21]	Tiotropium 18 μg qd/placebo	3.5/3.6	NR	NR
Tashkin et al (2008) (UPLIFT)[22]	Tiotropium 18 μg qd/placebo	1.7/0.9[a]	1.6/1.3[a]	2.1/2.0[a]
Troosters et al (2014)[23]	Tiotropium 18 μg qd/placebo	1.3/0.9	NR	NR
Kerwin et al (2012) (GLOW2)[27]	Tiotropium 18 μg qd OL/placebo	1.5/1.9	NR	6.0/3.0
Tiotropium (via Respimat® device)				
Bateman et al (2010)[24]	Tiotropium 5 μg qd/placebo	7.2/2.1	NR	NR
Bateman et al (2010)[25]	Tiotropium 5 μg qd/placebo	3.1/1.4	NR	NR
Glycopyrronium				
D'Urzo et al (2011) (GLOW1)[26]	Glycopyrronium 50 μg qd/placebo	NR	NR	NR
Kerwin et al (2012) (GLOW2)[27]	Glycopyrronium 50 μg qd/placebo	3.0/1.9	NR	2.7/3.0
Umeclidinium				
Donohue et al (2013)[28]	Umeclidinium 62.5 μg qd/placebo	NR	NR	NR
Aclidinium				
Jones et al (2012) (ATTAIN)[29]	Aclidinium 400 μg bid/placebo	NR	NR	0.7/0.7
Singh et al (2014) (ACLIFORM)[30]	Aclidinium 400 μg bid/placebo	NR	NR	NR
D'Urzo et al (2014) (AUGMENT)[31]	Aclidinium 400 μg bid/placebo	0.6/0.3	2.1/1.8	3.3/3.0

Notes: [a]Incidence rate per 100 patient years.
Abbreviations: AEs, adverse events; bid, twice daily; LAMA, long-acting muscarinic antagonist; NR, not reported; OL, open label; qd, once daily; UTI, urinary tract infection.

in corresponding SmPCs reported dry mouth in 4% of patients receiving tiotropium (HandiHaler®), 2.9% of patients receiving tiotropium (Respimat®), and 2.2% of patients receiving GLY; specific information was not provided in umeclidinium or aclidinium SmPCs.[8–11] Therefore, LAMA safety profiles appear to be acceptable in the trial patients.

Comparisons between LAMAs

Results presented here are from separate studies with different settings and designs and are therefore not directly comparable. In the absence of head-to-head studies, comparisons of results from separate studies should be viewed with caution. However, head-to-head comparisons of LAMA therapies have shown some differences, notably the faster onset of action of GLY vs tiotropium.[27,54] In GLOW5, GLY increased FEV_1 by 51 mL compared with tiotropium at 5 minutes postdose and by 63 mL at 15 minutes postdose on day 1 ($P<0.01$).[54] In GLOW2, GLY increased FEV_1 by 143 mL vs placebo at 15 minutes postdose ($P<0.001$) and almost doubled the response seen with tiotropium at that timepoint (78 mL). Any perceivable benefit observed by the patient following the first dose of medication may be lost following subsequent maintenance doses,[55] however, may become relevant again when patients do not adhere to daily maintenance treatment, a problem well documented in COPD patients. In a systematic review and network meta-analysis examining the comparative efficacy of LAMAs in COPD, changes from baseline in trough FEV_1 at 12 weeks favoring GLY, aclidinium, and umeclidinium vs tiotropium were found; however, the study concluded that these agents had at least comparable efficacy to that of tiotropium.[56]

GLY, tiotropium, and aclidinium had similar effects on measures of lung function, dyspnea, health status, and exacerbations.[27,54,57] In GLOW2, GLY and tiotropium reduced the risk of first moderate-to-severe exacerbation to a similar extent vs placebo (34 and 39%, respectively, both $P=0.001$).[27] GLY significantly reduced the rate of moderate-to-severe exacerbations by 34% compared with placebo (0.54 vs 0.80 per year; rate ratio [RR] 0.66; 95% confidence interval [CI] 0.496–0.821; $P=0.003$). GLY and open-label tiotropium had similar efficacy in reducing all exacerbations (RR 1.01) and improving lung function and health status in a 64-week study of 1,483 patients with COPD and severe-to-very severe airflow limitation.[58,59] A network meta-analysis demonstrated aclidinium to be at least comparable to GLY and tiotropium in terms of trough FEV_1, health status (assessed by SGRQ with the proportion of responders achieving at least a four point improvement), and dyspnea (assessed by TDI score

where the majority of responders achieved at least a one point improvement).[57] In a pooled analysis, aclidinium also reduced the rate of exacerbations of any severity and moderate-to-severe exacerbations by ~20% compared with placebo, which is consistent with the other LAMAs.[60]

Discussion

Relevance of the study populations to clinical practice

The clinical studies reviewed were conducted mostly in patients with moderate-to-severe airflow limitation (GOLD grade II or III), this is likely similar to the patient population in clinical practice.[61–64] Most studies included a small percentage of patients with very severe airflow limitation (GOLD grade IV) and excluded patients with mild airflow limitation (GOLD grade I) as well as hypoxemia on long-term oxygen therapy. The GOLD 2018 stepwise ABCD treatment approach is based only on symptoms and exacerbation risk (as opposed to former recommendations based on the severity of airflow limitation).[1]

Patients with life-threatening comorbid conditions that could interfere with study results are excluded from clinical studies.[65] However, physicians can expect to see a range of comorbidities in COPD patients in clinical practice, including cardiovascular disease, anxiety/depression, asthma, diabetes, kidney disease, and chronic pain.[12,62] One study estimated that ~98% of COPD patients had ≥1 comorbidity, while ≥50% of them have ≥4 comorbidities.[66] The DACCORD (Outpatient Care with Long-Acting Bronchodilators: COPD Registry in Germany) ongoing noninterventional study estimated a lower value of 78.3%.[64,66] More trials will attempt to include a wider range of patients with COPD to accurately reflect the prevalence of comorbidities in the real world.[67] Supplementary medications to treat comorbidities increase the risk of unwanted drug interactions and AEs, potentially altering a patient's compliance to treatment.[68] Therefore, physicians need to remain aware of the above factors and use their judgment to assess the risk–benefit profile of each treatment before arriving at an appropriate decision.

Efficacy of LAMAs in clinical practice

FEV_1 was the most common primary outcome measure of lung function in the studies reviewed, as suggested by the United States Food and Drug Administration (FDA) and EMA. Other patient-reported outcome (PRO) measurements such as breathlessness, health status, and exacerbation provide a robust basis for evaluating the potential benefits of LAMAs. The data discussed suggest that LAMAs improve lung function, dyspnea, and health status compared with placebo.

COPD patients often reduce their daily activities according to symptom intensity and may not perceive full treatment benefit unless encouraged to increase activity levels. Notably, increased exercise capacity does not necessarily result in enhanced physical activity and some experimental methods are not representative of real-life exercise capacity.[69]

Exacerbations are associated with a poor prognosis in terms of health status,[70,71] lung function decline,[72,73] and mortality risk.[74,75] Therefore, prevention of COPD exacerbations is an important treatment goal.[1] Among the LAMAs reviewed, GLY and tiotropium had the most evidence supporting a beneficial effect on exacerbations; both significantly prevented or reduced the rate of moderate-to-severe exacerbations compared with placebo in studies of >1 year.[22,24,25,27] Umeclidinium and aclidinium have yet to be assessed in a study of >24 weeks and appropriately powered to eliminate seasonal influences and test for differences in exacerbations.[28–30]

LAMA and LABA monotherapies appear to have a similar effect on FEV_1 and symptom relief.[4] POET demonstrated that the LAMA tiotropium was more effective than the LABA salmeterol at reducing exacerbation risk,[6] which may be due to the presence of patient subgroups with polymorphisms of the β_2-adrenoceptor that affect the response to LABA treatment.[76] While GOLD recommends LAMAs as a treatment strategy for exacerbation prevention, it gives no treatment preference for symptom relief.[1]

Only one study prospectively evaluated a LAMA as initial (and sole) maintenance therapy in patients with GOLD grade II COPD who were treatment naive. The objective was to evaluate the difference between tiotropium vs placebo on FEV_1. Tiotropium significantly improved lung function and PROs compared with placebo.[23] Other studies permitted the concomitant use of ICS, as suggested by GOLD,[1] and therefore may not give a clear indication of the efficacy of bronchodilator monotherapy. It is not clear whether ICS treatment was appropriate in these patients since current knowledge suggests that ICS may only be effective in preventing exacerbations in a subgroup of patients with COPD.[77] However, a pooled analysis of data from two GLY studies showed a similar efficacy of GLY and tiotropium on lung function and exacerbation outcomes in patients regardless of ICS use.[78]

Combining the two classes of bronchodilator results in improvements in lung function, dyspnea, health status, rescue medication use, and exacerbations compared with LAMA monotherapy.[58,79–84] For patients with persistent symptoms

on monotherapy, LABA/LAMA therapy is recommended while patients with severe symptoms should consider dual bronchodilation as initial treatment.[1] In BLAZE, IND/GLY significantly improved dyspnea, lung function, and rescue medication use compared with placebo and tiotropium monotherapy in symptomatic patients (modified Medical Research Council [mMRC] dyspnea scale >2).[84] In addition, in a post hoc analysis of SHINE, LABA/LAMA significantly improved dyspnea and lung function compared with tiotropium in patients with moderate-to-severe dyspnea.[83] In patients with a history of ≥1 exacerbation in SPARK, IND/GLY significantly reduced the rate of moderate-to-severe COPD exacerbations compared with GLY and the rate of all exacerbations vs GLY and tiotropium.[58] INSPIRE reported similar effects on exacerbation reduction for tiotropium and salmeterol/fluticasone propionate (SFC) in patients with a history of exacerbations.[85] Furthermore, FLAME demonstrated that IND/GLY was significantly more effective than SFC in preventing all and moderate or severe exacerbations in patients with a history of ≥1 exacerbation.[86] Therefore, GOLD recommendations for ICS/LABA use are limited to an alternative to LABA/LAMA and for patients with features of asthma–COPD overlap (ACO).

LAMAs are often used in conjunction with ICS/LABA, commonly referred to as triple therapy.[12] Several studies have demonstrated the superiority, in terms of lung function, of combinations of ICS, LABA, and LAMA over ICS/LABA.[14,87] If exacerbations persist despite LABA/LAMA or ICS/LABA therapy in GOLD Group D patients, GOLD recommends stepping up to triple therapy.[1] Indeed, clinical trial evidence supporting this recommendation is beginning to emerge from studies such as TRILOGY (which assessed beclometasone dipropionate, formoterol fumarate, and GLY), FULFIL, and IMPACT (assessing fluticasone furoate, umeclidinium, and vilanterol).[14,87,88]

Studies show ICS providing a small, clinically insignificant increase in lung function (32–48 mL) when used in combination with LABA compared with LABA monotherapy,[78–80] but this increase achieved statistical significance ($P<0.001$) in only one of the three studies.[80] Similarly, WISDOM (Withdrawal of Inhaled Steroids during Optimized Bronchodilator Management) demonstrated a statistically significant decrease in trough FEV_1 following complete ICS withdrawal compared with ICS continuation (43 mL, $P=0.001$) in patients with severe-to-very severe airflow limitation and ≥1 exacerbation in the previous year.[89] Comparing this with the improvement when one bronchodilator is added to another (120–168 mL), any benefit seen with triple therapy vs one bronchodilator only may be driven mainly by dual bronchodilation. GOLD recommends ICS for patients with an exacerbation history (GOLD Groups C and D), yet they are prescribed to patients in all GOLD Groups. Further investigation is therefore needed to identify reasons why large numbers of primary care patients have been inappropriately escalated to or initiated on ICS/LABA therapy, to better understand the right population eligible for triple therapy and to elucidate any benefit of ICS over LABA/LAMA in triple therapy, data that are not yet available.[90–92] If ICS treatment has been inappropriately prescribed, WISDOM demonstrated that ICS can be withdrawn from triple therapy in patients with severe-to-very severe COPD with a low baseline exacerbation rate without an increase in the risk of exacerbation provided adequate bronchodilator therapy is in place.[93]

As GOLD guidance is limited regarding which patients should receive ICS treatment, it has become apparent that phenotyping, subgrouping, and/or endotyping can help tailor the management of a patient with COPD ensuring they get the appropriate treatment they need.[94] One study found that inflammatory phenotypes, such as frequent exacerbators, patients with chronic bronchitis, and those with a number of comorbidities, needed ICS treatment,[94] whereas patients with emphysema required dual bronchodilation.[94] The GesEPOC guidelines also propose treatment approaches based on clinical phenotypes, but without evidence base.[15] For example, roflumilast is recommended in patients with an exacerbator phenotype and chronic bronchitis, as well as antibiotic therapy guided by sputum purulence in hospitalized patients with COPD exacerbations.[15]

Blood eosinophils may further help determine which patients may benefit from ICS treatment, with post hoc analyses suggesting a greater benefit of ICS/LABA vs LABA monotherapy in patients with elevated blood eosinophils vs those with lower blood eosinophil counts.[95–97] However, given the nature of available evidence, which arises predominantly from post hoc analyses,[86,98] although data exist from a prospective analysis of FLAME, eosinophil-guided ICS treatment for COPD exacerbations is currently a controversial area.[86,98] Using clinical phenotypes and biomarkers as a form of personalized medicine could be highly valuable to clinical practice, as it enables predictions to be made regarding which patients will respond well to certain classes of drugs.[99,100]

Inhaler selection

Detailed consideration of the characteristics of the different LAMA delivery inhalers is summarized in Table 6.[8–11,101–106] Given the fact that patients receive intensive education on the

Table 6 Inhalers used with LAMAs for COPD

Property of inhaler	HandiHaler®[9,101]	Respimat®[8,102,103]	Breezhaler®[10,101]	Ellipta®[11,104,105]	Genuair®[9,106]
LAMA administered	Tiotropium	Tiotropium	Glycopyrronium	Umeclidinium	Aclidinium
Single dose or multidose	Single dose	Multidose	Single dose	Multidose	Multidose
Type	Dry powder	Soft mist (spray)	Dry powder	Dry powder	Dry powder
Resistance	High	Low	Low	Medium	Medium
Inhalations for each use	One capsule[a]	Two actuations	One capsule[b]	One	One
Dose counter	N/A	Dose indicator shows approximately how much left	N/A	Yes (on opening cover)	Dose indicator (counts in intervals of 10)
Confirmation of dose	No (capsule is opaque but can be opened)	No	Yes (hear the click when the capsule is pierced and the whirring sound during inhalation; feel the lactose in the product; see the clear/empty capsule)	Yes (clicking sound when cover is opened and dose is ready; counter counts down by one)	Yes (green control window confirms that product is ready for inhalation – this turns back to red to confirm that full dose has been taken; clicking sound signals correct inhalation)
Locks when empty	N/A	Yes	N/A	No	Yes
Refillable	Yes (clean monthly; replace after 1 year)	No (replace if empty)	Yes within the same prescription. Each inhaler should be replaced after 30 days of use	No (replace if empty)	No (replace if empty)

Notes: [a]Second inhalation required to ensure the capsule is empty. [b]More than one inhalation may be required to empty the capsule; most people are able to empty the capsule with one or two inhalations.
Abbreviations: LAMA, long-acting muscarinic antagonist; N/A, not available.

use of COPD delivery inhalation devices, randomized controlled trials are not considered suitable for the examination of whether inhaler choice affects clinical outcomes. Nevertheless, one study demonstrated that critical error rates irrespective of inhaler type were associated with severe COPD exacerbations, indicating that training patients in the use of inhaler devices is an essential aspect of treatment efficacy.[107] The impact of the inhaler on treatment adherence, which may be as poor as 50% in clinical practice among patients with COPD, should also be considered.[108,109] Therefore, patient satisfaction with their inhaler is likely to encourage treatment adherence and impact clinical outcomes.[110,111]

A recent study analyzed the relative importance of different attributes of a once-daily dosing inhaler device, determined by patients with ≥6 months COPD: patients cited ease of use, dose delivery recording, and dose capacity (multi- vs single-dose devices) as the most important attributes.[112] Conjoint analysis indicated that attributes related to device characteristics accounted for 88% of the relative importance patients placed on the device, whereas the number of doses each day accounted for 12% of the relative importance.[112] However, evidence suggests that the majority of patients prefer a once-daily dosing regimen compared with multiple daily dosing,[113] even if device characteristics are ranked higher in importance. In contrast, frequency of dosing is known to inversely affect treatment adherence.[114] However, some patients with severe COPD may be familiar with twice-daily treatment regimens and may psychologically prefer this to a once-daily schedule, particularly those suffering from severe morning and nighttime symptoms. Different factors govern inhaler preference in individual patients; if problems seem insurmountable with one inhaler, there should be a low threshold for switching to an alternative LAMA/inhaler.

Internal resistance varies between different inhaler devices and can affect both ease of inhalation and drug deposition.[115] Data on inhaler resistance are from in vitro studies, and their importance and applicability in certain real-life situations are unclear.

Furthermore, studies have assessed the relative patient preference for currently available dry powder inhalers with variable results.[116–119] Prescribers should take an active role in teaching their patients the correct inhalation technique for each device at initial assessment. Frequent follow-up and monitoring are critical to ensure that efficacy is sustained, especially in patients with very severe airflow limitation. The significance and benefits of these real-life assessments for physicians and patients in clinical practice outweigh the relevance of experimental data.

Additionally, for patients receiving treatment with a single bronchodilator, choice of initial therapy may be influenced by the availability of a dual bronchodilation fixed-dose combination (FDC) containing the same agent and administered via the same delivery device, should the patient subsequently require additional COPD treatment. Therefore, receiving monotherapy or FDC therapy from a single type of inhaler may be advantageous in terms of convenience and potentially adherence and dosing regimens should be considered to allow the combination of different drugs into the same inhaler to prevent patient confusion.

The importance of distinguishing between asthma and COPD

Many patients with COPD meet the FEV_1 reversibility criteria required for asthma diagnosis.[120] This may result in disease misclassification if a thorough clinical history is not taken during initial patient assessment. As long-acting bronchodilator monotherapy is not recommended for the treatment of patients with asthma,[121] it is crucial that clinicians are comfortable distinguishing between COPD and asthma.[2,3] It is tempting to speculate that the overuse of ICS in COPD may be in part driven by the challenge that physicians face in distinguishing between these conditions.[77]

Summary and conclusion

The 14 fully published, randomized, placebo-controlled studies analyzed here demonstrate that LAMA therapy results in clinically meaningful improvements in lung function and health status, as well as significant reductions in COPD exacerbations and breathlessness when compared with placebo. At present, the greatest weight of evidence exists for tiotropium and GLY, particularly in terms of effects on exacerbations. The few head-to-head studies of GLY and aclidinium vs tiotropium demonstrated generally comparable efficacy in terms of lung function, dyspnea, exacerbations, and health status, with few apparent differences in safety profiles between available LAMAs. Differences exist between the devices used to deliver each LAMA, which may be important to individual patients as well as once- or twice-daily treatment regimen. Therefore, an appropriate choice of initial LAMA therapy should involve individual physician's and patient's experiences and preferences, as well as consideration of patient comorbidities. Furthermore, the availability of a FDC product containing the same agent and using the same device should be considered for the potential future escalation of treatment. Overall, the evidence discussed demonstrates that LAMAs provide effective and generally well-tolerated maintenance therapy for patients with COPD, indicating that these agents can be used with confidence and as first choice in patients typically seen in primary practice.

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Author contributions

Authors discussed and agreed to the scope of the article, elaborated the layout of the review and contributed to the development of the article at all stages. All authors contributed toward data analysis, drafting and revising the paper and agree to be accountable for all aspects of the work. All authors read and approved the final article.

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