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Assessing the clinical value of fast onset and sustained duration of action of long-acting bronchodilators for COPD

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ABSTRACT

The long-acting inhaled bronchodilators available for use in chronic obstructive pulmonary disease (COPD) vary in their pharmacological class (β_2-adrenergic agonist or antimuscarinic/anticholinergic, alone or combined), durations of action and speed of onset of bronchodilator effect. In the early stages of development of a maintenance bronchodilator, the goals are to identify a molecule with the theoretically 'ideal' profile of fast onset and prolonged duration of action in comparison with existing agents, while minimizing non-specific activity at organs outside the lungs. The move towards increasing duration of bronchodilator action is generally paralleled by improved effects on clinical outcomes, and the advent of more potent agents seems likely to provide an opportunity to reduce overreliance on the use of inhaled corticosteroids in treating COPD. In terms of onset of action, an immediately perceived benefit in reducing dyspnea, although not definitively demonstrated, might prove useful in increasing adherence, which is very poor among patients with COPD. Once-daily administration may also be helpful in this respect. Shared decision-making between patient and physician in the choice of treatment is important in optimizing adherence and, thus, treatment effectiveness.

1. Introduction

Pharmacological treatment of chronic obstructive pulmonary disease (COPD) is used to improve lung function, thereby alleviating symptoms, reducing exacerbations and improving health status and exercise tolerance [1]. These aims hold true for each of the main treatment options available, namely long-acting bronchodilators (long-acting β_2-adrenergic agonists [LABA] and long-acting muscarinic antagonists [LAMA]), inhaled corticosteroids (ICS; used only in combination with β_2-adrenergic agonists for COPD) and the various combinations of these agents. In the treatment of COPD, inhaled long-acting bronchodilators provide effective treatment against the outcomes listed above, including exacerbations and exercise tolerance, through mechanisms of increased airway patency and reduced hyperinflation [2,3]. While no treatment has been proven conclusively to reduce the accelerated decline in lung function that characterizes COPD, post-hoc analyses have reported a slower loss of lung function during treatment with long-acting bronchodilators and ICS/LABA combinations, compared with placebo, in patients with moderate-to-severe COPD [4,5].

Characteristics of an ideal new bronchodilator should include longer duration of action, with at least a 24-h sustained bronchodilator effect allowing once-daily dosing, a fast onset of bronchodilator action at least similar to that of salbutamol (thus minimizing undue reliance on rescue medication), and a favorable safety and tolerability profile [6]. An increasing number of long-acting bronchodilators have become available in recent years. Their efficacy has generally advanced in line with increasing duration of action (short-to long-acting [7]; twice-to once-daily [8,9]) and potency of bronchodilation (mono-to combination therapy [10]), without any added safety concerns [7–9,11].

Given the current or imminent availability of several long-acting bronchodilators for use in patients with COPD, is it important or

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necessary to distinguish between them? In this article, we compare the onset and duration of action of long-acting bronchodilators for COPD and consider whether the theoretical 'ideal' profile translates into practical and clinical advantages for patients. Data on onset and duration were obtained from a search of the literature on PubMed for the currently used long-acting bronchodilators in COPD (in English; no date restrictions), with preference given to data from phase III studies using approved doses.

2. Comparative pharmacological characteristics of currently available long-acting bronchodilators

2.1. Long-acting β_2-adrenergic agonists (LABAs)

β_2-adrenergic receptors are present in high concentrations in the smooth muscle of the lungs, predominantly the small airways. They are coupled to an intracellular G-protein (G_s), which is stimulated when the agonist interacts with the β_2-adrenoceptor. This sets off an intracellular signaling reaction with production of adenylyl cyclase increasing cyclic adenosine monophosphate (cAMP), leading to a fall in intracellular calcium levels, and the opening of large-conductance potassium channels. This causes hyperpolarization and relaxation of airway smooth muscle [12]. However, it has become increasingly clear that signaling through adenylyl cyclase-coupled pathways is considerably more complex and sophisticated than was considered previously, and there is still little known regarding these pathways in airway cells [13].

Several factors determine onset of effect of LABAs after delivery by inhalation. One is the time taken to reach effective concentrations at the local receptor site, with diffusion rates determined by physico-chemical properties of the drug molecule. The more lipophilic the molecule, the slower the onset; a degree of water solubility, allowing rapid diffusion into intracellular spaces, is needed for a faster onset [14,15]. High intrinsic efficacy (full agonism) at the receptor promotes a fast rate of cAMP accumulation, and this may explain the fast onset of action of some relatively lipophilic β_2-adrenoceptor agonists [16,17]. Some pharmacological properties of the various agents are summarized in Table 1 [18]. Formoterol and indacaterol have similar, high intrinsic efficacy at the β_2-adrenoceptor: 95% and 86%, respectively, relative to isoprenaline (100%). Vilanterol is somewhat lower at 70%, but still higher than salmeterol (41%) [18]. Olodaterol is reported to have 88% intrinsic efficacy at the β_2-adrenoreceptor and a potency (pEC_{50} = 9.93) similar to that of salmeterol (9.90) and formoterol (9.73) [19]. Potency in electrical field stimulated human bronchial rings (pEC_{50} = 9.49) was similar to that of formoterol (9.73) [19]. Preclinical studies with olodaterol report that its onset of action is comparable to formoterol, with maximal bronchoprotection after inhalation of a single dose of olodaterol or formoterol reached within 3–6 min in guinea pigs and 10 min in dogs [19].

Table 1
In-vitro characterization of β_2-adrenergic agonists: potency, onset and intrinsic efficacy data [18].

β_2-adrenergic agonist	EFS guinea pig trachea model		cAMP detection assays (β_2-adrenoreceptor)	
	Potency (pEC_{50})	Onset $t_{½}$ (min)	Potency (pEC_{50})	Intrinsic efficacy (β_2)[a]
Vilanterol	8.62 ± 0.27	5.8 ± 0.5	10.37 ± 0.05	0.70 ± 0.03
Salmeterol	6.84 ± 0.03	15.2 ± 0.6	9.80 ± 0.10	0.41 ± 0.01
Formoterol	8.56 ± 0.18	4.0 ± 0.1	10.14 ± 0.08	0.95 ± 0.04
Indacaterol	6.84 ± 0.16	4.0 ± 0.2	9.48 ± 0.08	0.86 ± 0.02

[a] Relative to isoprenaline (=1). cAMP, cyclic adenosine monophosphate; EFS, electrical field stimulated; pEC_{50}, negative logarithm of the half-maximal effective concentration; $t_{½}$, half-life; ND, not determined. Data from Ref. [18].

The relevance of low intrinsic efficacy (partial agonist activity) is unclear, particularly for COPD. All the β_2-adrenergic agonists have some (unwanted) activity at the β_1-adrenoceptor. It has been claimed that partial agonist activity at the β_1-adrenoreceptor may result in fewer cardiovascular side effects [19], but many other factors such as binding kinetics are likely to be involved. If receptor numbers are low or receptors are not working efficiently, a partial agonist will have a lower maximal effect than a full agonist and may even act as an antagonist in the presence of a full agonist. Partial agonist properties do not affect bronchodilator efficacy, but might reduce the ability of that agent or a rescue bronchodilator to reverse acute severe bronchospasm [14,20,21]. Whether the degree of intrinsic efficacy relates to tolerance or desensitization to β_2-mediated effects in long-term clinical use is unknown; again, other factors will be important, such as receptor reserve and transduction efficiency in airway smooth muscle cells [22–24].

It is unclear why LABAs are able to cause such long bronchodilation, and several contrasting hypotheses have been formulated [12]. First, the anchored binding (or exosite) hypothesis suggests that a long lipophilic tail (e.g. of salmeterol) may bind to a region of the β_2-adrenoceptor that is apart from the active receptor site, anchoring the drug to or near the receptor and allowing repeated receptor activation [25]. Second, a molecule with a degree of lipophilicity will provide a depot of drug at the receptor site by partitioning into lipid regions and cell membranes [26]. An extension to this 'diffusion microkinetics' model describes partitioning of drug into lipophilic compartments ('lipid rafts') on airway smooth muscle cell membranes, where β_2-adrenoceptors are in close contact with signaling and effector molecules, and has been proposed to account for the duration of action of indacaterol [27,28]. Third, tight binding to the β_2-adrenoceptor and formation of a ternary complex with a long dissociation half-life was proposed for olodaterol [29], but dissociation half-life alone is unlikely to account for duration of action [18].

2.2. Long-acting muscarinic antagonists (LAMAs)

Muscarinic antagonists are also described synonymously as antimuscarinics or anticholinergics. These agents block the effects of the endogenous cholinergic bronchoconstrictor acetylcholine, thus resulting in bronchodilation. Acetylcholine acts on a family of five G-protein-coupled muscarinic receptors (M1 to M5), of which the M_1 to M_3 subtypes are expressed in the airways [30]. M_1 receptors are found in parasympathetic ganglia where they facilitate neurotransmission. M_2 receptors occur presynaptically on airway smooth muscle and downregulate acetylcholine release while capturing released acetylcholine (autoregulation). In addition, M_2 receptors on airway smooth muscle couple preferentially to the G-protein isotype $G_{\alpha o/i}$, and function to counteract the β_2-adrenoceptor-mediated relaxant pathway by inhibiting the generation and accumulation of cAMP [31–33]. In the heart, M_2 receptors are present post-synaptically and mediate effects such as tachycardia [30]. M_3 receptors are expressed on airway smooth muscle, submucosal mucus glands and vascular endothelium. Pharmacological studies have indicated that under normal conditions contraction in both central and peripheral airways is mediated primarily by the M_3 receptor [34].

Thus, the ideal profile for a LAMA for COPD management is one in which M_3 receptor blockade outweighs its activity at the M_2 receptor in order to provide a favorable efficacy:safety ratio [12]. The LAMAs achieve this through kinetic selectivity, whereby dissociation from M_3 receptors is slower than from M_2 receptors (see Table 2). Compared with the other LAMAs listed, glycopyrronium has the most favorable ratio of M_3:M_2 receptor residency time, although whether the apparent advantage of

Table 2
Comparison of LAMA receptor binding: dissociation rate constants and half-lives at human M_2 and M_3 muscarinic receptors. (From Ref. [37], with data from a separate study on umeclidinium and tiotropium from Ref. [38]).

	M2		M3		t½ M_3/M_2
	K_{off} (h^{-1})	$t_{½}$ (h)	K_{off} (h^{-1})	$t_{½}$ (h)	
Tiotropium [37].	0.26 ± 0.05	2.6	0.026 ± 0.005	27	10.4
Aclidinium [37].	0.39 ± 0.03	1.8	0.071 ± 0.01	10.7	5.9
Glycopyrronium [37].	1.84 ± 0.1	0.37	0.11 ± 0.02	6.1	16.5
	K_{off} (min^{-1})	$t_{½}$ (min)	K_{off} (min^{-1})	$t_{½}$ (min)	
Tiotropium [38].	0.023 ± 0.008	39.2 ± 9.7	0.0026 ± 0.0003	272.8 ± 27.6	7.0
Umeclidinium [38].	0.074 ± 0.004	9.4 ± 0.5	0.0089 ± 0.0012	82.2 ± 0.0012	8.7

K_{off}, rate constant of dissociation of radiolabelled antagonist; $t_{½}$, residence half-life.

glycopyrronium vs the other agents translates into improved clinical efficacy and safety remains to be established.

Receptor kinetics may also explain differences in onset of action, in terms of time taken to achieve equilibration at the M_3 receptor. The predictions from simulated kinetic rate constants that tiotropium would take four to five times longer than glycopyrronium to equilibrate with the M_3 receptor at equi-effective concentrations were confirmed in the in-vitro calcium assay (glycopyrronium was 5-fold faster) and the rat tracheal strip assay (2.5-fold) [35].

However, slow dissociation from the M_3 receptor does not appear to explain fully the duration of action of the LAMAs. M_3 dissociation rates of glycopyrronium and tiotropium were reduced 3-fold under physiological conditions, compared with under non-physiological conditions, to a level that was incompatible with their known 24-h duration of action [35]. A process of rebinding of freshly dissociated drug was proposed with respect to these agents, perhaps through micro-anatomical constraints at a local tissue level that restrict the free diffusion of drug molecules away from the local environment where the receptors are concentrated [35,36].

2.3. Combination of LABA and LAMA

A synergistic (i.e. more than additive) bronchodilator effect of a LABA and LAMA has been demonstrated in airway preparations in vitro and in patients with COPD [39,40]. These preliminary studies support the scientific rationale for combining the two types of drugs but preclinical data investigating synergy are limited and further work is required. In theory, a synergistic effect may be explained by removal of the bronchoconstrictor effects of acetylcholine by the antimuscarinic, allowing an amplified β_2-adrenergic-agonist-induced bronchodilation [31], and also by interactions between the post-receptor intracellular signaling pathways for M_3 and β_2-adrenoreceptors, resulting in an overall amplification of effect [34,41]. This forms the mechanistic basis for treating patients with COPD with a combination of bronchodilators that have different mechanisms of action. Whether such synergism is relevant to increasing the speed of onset or prolonging the duration of bronchodilator effect is unknown.

3. Onset and duration of effect of long-acting bronchodilators

Onset and duration of a bronchodilator are properties that have not been defined formally in clinical terms. Onset of effect may be expressed in various ways, usually the earliest time at which a significant effect is achieved vs placebo, or the time taken to reach a particular level of bronchodilation (e.g. 100 or 200 mL, or 12% or 15% increase from baseline). Other possibilities are time to peak effect, or time to half-maximal effect. The effect is usually expressed in terms of forced expiratory volume in 1 s (FEV_1). Onset may also describe a statistically or clinically significant bronchodilator effect on day 1 of treatment, which is achieved by some of the current long-acting bronchodilators. Most LABAs and LAMAs take about 1 week to achieve pharmacokinetic steady state (up to 2–3 weeks with indacaterol and tiotropium), but any difference in bronchodilator effect between first dose and steady state will also depend on other factors such as the degree of accumulation of drug during this time, and the nature of the relationship between pharmacokinetic and pharmacodynamic variables [42]. Glycopyrronium takes 1 week to achieve pharmacokinetic steady state but pharmacodynamically achieves its full bronchodilator effect after the first dose [43–45] (see Table 3).

Duration of effect and dosing interval or frequency (e.g. once or twice daily) are not necessarily the same but are closely interrelated and are a function of maintenance dose and pharmacokinetics. The development of the once-daily bronchodilators reviewed here had from the outset the aims of designing a molecule with long-acting bronchodilating properties that would prove suitable for once-daily dosing, with initial clinical studies confirming safety, tolerability and pharmacokinetics. Dose-ranging clinical studies, usually measuring lung function, were then employed to establish the minimum effective doses given once- or sometimes twice-daily [46]. Duration of effect can be dose-dependent [47]. Aclidinium was originally investigated as a once-daily drug given at doses of 200 or 400 μg but was found to be suboptimal in terms of effect size and duration; 400 μg twice daily showed greater efficacy than the 200 μg dose and this regimen was approved for use [48]. Regulatory perspectives on what constitutes a minimum effective dose may vary, resulting in the approval of different doses and regimens of a given drug at different times and in different regions; for example, indacaterol is approved at a once-daily dose of 75 μg in the USA and at doses of 150 and 300 μg in other countries. On the other hand, the older drug formoterol, introduced in 1990, was approved for use twice daily, yet its bronchodilator effect may last for only 6 or 8 h post-dose [49].

In clinical drug trials in COPD, duration of bronchodilator effect may be the length of time post-dose during which a statistically significant and/or clinically important bronchodilator effect on FEV_1 in relation to placebo is maintained, either in absolute terms or as relative change from baseline. A 100 mL difference in pre-dose or trough FEV_1 has been reported as the minimum clinically important difference that is perceptible to patients [50]. Bronchoprotection is often used as a measure of duration of effect in asthma, but has no corollary in COPD.

Both onset and duration are typically assessed in terms of changes over time in FEV_1, which is widely used, easy to measure, and a required variable in regulatory clinical drug trials. In the specialized setting, a more comprehensive assessment of bronchodilator effects can be obtained using sensitive methods such as oscillometry and body plethysmography [51]. FEV_1 may be insensitive to some important physiological abnormalities in COPD, such as hyperinflation [52]. However, the relevant measures of lung volume require

Table 3
Onset of bronchodilator effect.

		FEV_1 difference vs placebo at 5 min post-dose (mL)[a]	Other onset variable (time is post-dose)[a]	Ref.
SABAs	Salbutamol 200 μg	90 (95% CI 60, 120)	7.9% (95% CI 5.5, 10.3) increase at 5 min vs placebo 36% of patients with ≥12% increase at 5 min vs baseline 23% of patients with ≥12% and >200 mL increase from baseline	[56]
Twice-daily LABAs	Formoterol 12 μg	140 (95% CI 120, 160)		[57]
		–	10% decrease of R_{aw} at 1.4 ± 0.9 min	[58]
		–	7.2% increase in FEV_1 at 5 min vs predose 23% of patients with ≥12% increase in FEV_1 at 5 min	[59]
	Salmeterol 50 μg	60 (95% CI 40, 80)		[9]
		–	10% decrease of R_{aw} at 15.1 ± 34.5 min	[58]
		–	4.1% increase in FEV_1 at 5 min vs predose 9% of patients with ≥12% increase in FEV_1 at 5 min	[59]
Once-daily LABAs	Indacaterol 150 μg	100 (95% CI 70, 130)	7.9% (95% CI 5.4, 10.3) increase at 5 min vs placebo 28% of patients with ≥12% increase from baseline at 5 min 19% of patients with ≥12% and >200 mL increase from baseline at 5 min	[56]
		120 (95% CI 100, 140)		[60]
		110 (95% CI 90, 130)		[9]
		–	FEV_1 $AUC_{0–4h}$: 160 mL increase vs placebo*	[10]
	Indacaterol 300 μg	120 (95% CI 90, 150)	10.1% (95% CI 7.7, 12.5) increase at 5 min vs placebo 46% of patients with ≥12% increase from baseline at 5 min 28% of patients with ≥12% and >200 mL increase from baseline at 5 min	[56]
		130 (95% CI 110, 150)		[57]
	Vilanterol 25 μg	69 (95% CI −8, 146)		[61]
		–	Time to ≥12% increase from baseline: 18 min Time to ≥100 mL increase in FEV_1 from baseline: 6 min	[62]
		–	131 mL increase in FEV_1 after 15 min vs placebo Time to ≥100 mL increase in FEV_1 from baseline: 27 min	[63]
		–	Time to ≥100 mL increase in FEV_1 from baseline 31 min	[64]
	Olodaterol 5 μg	118*		[65]
Twice-daily LAMAs	Aclidinium 400 μg	–	At 15 min: ~70 mL (est.) increase in FEV_1 vs placebo*	[66]
Once-daily LAMAs	Tiotropium 18 μg	45*[b]	At 15 min: 78 mL increase in FEV_1 vs placebo* FEV_1 $AUC_{0–4h}$: 141 mL increase vs placebo*	[67]
		60 (95% CI 30, 80)[b]		[60]
		–	sGaw 0.08 (0, 0.15) 1/kP*s vs placebo at 5 min FRC −200 mL (95% CI −340, −60) vs placebo at 5 min	[68]
		–	39 mL (95% CI 6, 71) from predose at 10 min ≥12% rise in FEV_1 after 79 min (95% CI 18, 140)	[69]
		–	~120 mL at 30 min (est.)	[70]
		–	FEV_1 $AUC_{0–4h}$: 140 mL increase vs placebo*	[10]
	Glycopyrronium 50 μg	93*	At 15 min: 144 mL increase in FEV_1 vs placebo* IC 181 mL vs placebo* at 25 min	[71]
		87*	At 15 min: 143 mL increase in FEV_1 vs placebo* FEV_1 $AUC_{0–4h}$: 197 mL increase vs placebo*	[67]
		–	FEV_1 $AUC_{0–4h}$: 190 mL increase vs placebo*	[10]
	Umeclidinium 62.5 μg	–	Time to increase in FEV_1 ≥100 mL above baseline: 56 min FEV_1 $AUC_{0–6h}$: ~135 mL (est.) increase vs placebo	[64]
LAMA/LABAs	QVA149 (indacaterol/glycopyrronium 110/50 μg)	126*	FEV_1 $AUC_{0–4h}$: 210 mL increase vs placebo*	[72]
		130*	FEV_1 $AUC_{0–4h}$: 220 mL increase vs placebo*	[10]
		–	sG_{aw} 0.21 (0.14, 0.29) 1/kP*s vs placebo at 5 min FRC −300 mL (95% CI −440, −160) vs placebo at 5 min	[68]
	Umeclidinium/vilanterol 62.5/25 μg	–	At 15 min: 112 mL increase in FEV_1 vs placebo Time to increase in FEV_1 ≥100 mL from baseline: 27 min	[64]

Values estimated from graphs are denoted by the '~' symbol and qualified as (est.). FEV_1 $AUC_{0–4h}$, FEV_1 averaged over 0–4 h post-dose; FRC, functional residual capacity; FEV_1 $AUC_{0–4h}$, area under the FEV_1 curve from 0 to 4 h; IC, inspiratory capacity; R_{aw}, airway resistance; sG_{aw}, specific airway resistance.
[a] Statistical significance denoted by *$p < 0.05$ or 95% confidence intervals.
[b] Open label.

relatively sophisticated equipment, and inspiratory capacity is often used as a surrogate measure of hyperinflation [3]. Measurements of airway resistance have been shown to correlate better than FEV_1 with acute bronchodilator-induced changes in dynamic hyperinflation, gas trapping, and dyspnea at rest [53]. Similarly, bronchodilator-induced improvements in exertional dyspnea have been observed in the absence of changes in FEV_1 [54,55].

Tables 3 and 4 compare the onset and duration of bronchodilator effect reported in clinical studies with the various long-acting agents. Salbutamol is included in Table 3 as an example of a fast-onset 'rescue' bronchodilator.

Among the LABAs, formoterol, indacaterol and olodaterol appear to share a fast onset of bronchodilator effect (Table 3). Although the available literature does not fully characterize all the

Table 4
Trough FEV_1 (difference vs placebo in mL [95% CI] unless otherwise stated) at 24 h post-dose[a] after first day's dosing, after 12 weeks and at last study day in clinical trials of long-acting bronchodilators.

		Day 1	Week 12	Last time point of study	Ref.
Twice-daily LABAs	Formoterol 12 μg	110 (90, 130)	70 (40, 100)	50 (10, 90) (wk 52)	[57]
	Salmeterol 50 μg	120	110	110 mL (wk 26)	[9]
		–	7.6% from baseline	6.2% from baseline	[73]
Twice-daily LAMAs	Aclidinium 400 μg	Not reported	105 change from baseline vs placebo	128 ± 22 change from baseline vs placebo (wk 24)	[74]
Once-daily LABAs	Indacaterol 150 μg	130	170	180 (wk 26)	[9]
		110 (80, 130)	180 (140, 220)	160 (120, 190) (wk 26)	[60]
		110 (90, 140)	150 (120, 180)	130 (100, 160) (wk 26)	[10]
	Indacaterol 300 μg	140 (110, 160)	170 (130, 200)	160 (120, 200) (wk 52)	[57]
	Vilanterol 25 μg	Not reported	Not reported	−30 from randomization[b] (wk 52)	[75]
		~90 (est.)	~90 (est.)	72 (32, 112) (wk 24)	[64]
		~105 (est.)	~100 (est.)	114 (wk 24)	[63]
		~105 change from baseline (est.)	~100 change from baseline (est.)	121 change from baseline (wk 24)	[76]
	Olodaterol 5 μg	Not reported	91	92 (wk 48)	[65]
		Not reported	47	68 (wk 48)	[65]
		Not reported	83	68 (wk 48)	[77]
		Not reported	59	44 (wk 48)	[77]
Once-daily LAMAs	Tiotropium 18 μg	100 (70, 120)[c]	140 (100, 180)[c]	140 (100, 180)[c] (wk 26)	[60]
		83[c]	83[c]	89[c] (wk 52)	[67]
		120 (90, 140)[c]	130 (100, 170)[c]	130 (90, 160)[c] (wk 26)	[10]
		Not reported	Not reported	120–150 (over 1 year)	[70]
		Not reported	Not reported	137 (wk 24)	[8]
	Glycopyrronium 50 μg	105	108	113 (wk 26)	[71]
		91	97 (65, 130)	108 (wk 52)	[67]
		110	120	120 (80, 150) (wk 26)	[10]
	Umeclidinium 62.5 μg	~105 (est.)	~135 (est.)	115 (76,155) (wk 24)	[64]
LABA/LAMAs	QVA149 (indacaterol/ glycopyrronium 110/50 μg	190 (170, 210)	230 (190, 260)	200 (170, 240) L (wk 26)	[10]
		Not reported	163	189 (wk 52)	[78]
	Umeclidinium/vilanterol 62.5/25 μg	~155 (est.)	~190 (est.)	167 (128, 207) (wk 24)	[64]
		~190 (est.)	~185 (est.)	211 (wk 24)	[76]
		~195 (est.)	~205 (est.)	208 (wk 24)	[76]

Values estimated from graphs are denoted by the '~' symbol and qualified as (est.).
[a] For the twice-daily agents, 12 h following the second dose of the day.
[b] ICS withdrawn at randomization.
[c] Open label.

LAMAs, glycopyrronium (NVA237) appears to have the fastest onset of action.

As shown in Table 4, the majority of bronchodilators have an effect on trough FEV_1 after the first day's dosing that is very close to or exceeds the reported minimal clinically important difference of 100 mL [50], the level at which patients may perceive a benefit, although results at this time point for olodaterol are not reported. On repeated dosing over several months, both olodaterol and vilanterol appear to have modest bronchodilator effects when viewed against results from studies with other long-acting agents. Comparing effects on trough FEV_1 at week 12 and a later (e.g. week 26 or 52) time point, there was a loss of effect with formoterol and a suggestion of a similar phenomenon, or at least inconsistent long-term effects, with vilanterol and olodaterol. Indacaterol generally maintained its effect over 1 year (Table 4). This apparent difference between LABAs may relate to the high intrinsic efficacy of formoterol, and maybe vilanterol. The process of β_2-adrenoreceptor desensitization with prolonged exposure to β_2-adrenergic agonist varies between cells, airway smooth muscle being less prone to the phenomenon than inflammatory cells (which may explain why tachyphylaxis in asthma manifests more commonly as loss of bronchoprotection rather than loss of bronchodilation) [21,79]. Tolerance to the typical β_2-mediated adverse events of tachycardia and tremor has been reported [21,80]. The LAMAs appear to have a consistent effect over time, with glycopyrronium and tiotropium maintaining trough FEV_1 at levels of 100 mL or more over 1 year. Studies with the newer LAMAs, aclidinium and umeclidinium, currently extend only up to treatment periods of 6 months. The combination LABA/LAMAs have a bronchodilator effect over time that is approximately 80–90% of the additive effect of the individual components [10,64].

Based on the data in Tables 3 and 4, indacaterol and glycopyrronium would figure prominently if a bronchodilator were to be chosen based on its rapid onset of bronchodilation, duration and magnitude of effect after a single dose, and persistence of bronchodilator effect during long-term use. However, whether their pharmacological advantages translate into superior benefits in terms of adherence, persistence or other patient perceptions remains to be demonstrated.

4. Benefits of fast onset of (bronchodilator) action

It might be expected that fast-onset bronchodilation would translate into fast relief of dyspnea (as in the case of salbutamol used as rescue medication). A recent study showed that changes in airway resistance (not FEV_1) 1 h after dosing with indacaterol 300 μg correlated with reductions in hyperinflation and gas trapping, and improvement in patient-reported dyspnea [53]. In a study comparing two fast-acting bronchodilators (formoterol and salbutamol) with the slower-acting salmeterol and oxitropium, the faster-acting agents induced a greater increase in FEV_1 and inspiratory capacity at 30 min post dose [81]. There was a significant correlation between acute bronchodilator effect and symptom improvement, which was strongest in patients with baseline

hyperinflation (Fig. 1). On repeated dosing, fast onset may not be particularly useful in patients who take their treatment regularly and have relatively stable symptoms. Conversely, it might be of help in patients with suboptimal adherence to treatment, since perceived rapid efficacy could reinforce compliance. It could also be useful in patients with more variable symptoms.

In some patients with COPD, symptoms vary over the day, with morning considered to be the time when symptoms are more severe [82]. It might be hypothesized that fast-acting agents could be more effective on these symptoms than those with a relatively slow onset of action, by providing rapid relief of symptoms after morning dosing [83]. In a 1-week crossover study, a twice-daily ICS/LABA containing budesonide and formoterol improved morning activities to a greater extent than twice-daily SFC [84] because of the faster onset of action of formoterol, compared with salmeterol. Similarly, in a 12-week study, the addition of the budesonide/formoterol combination to tiotropium resulted in increased FEV_1 immediately post-dose and an improvement in morning symptoms and activities, compared with tiotropium alone [85]. However, despite their possible association with poorer health status and more frequent exacerbations, it is not known if morning symptoms represent some kind of phenotype in that such symptoms might be particularly pronounced in some patients independently of overall clinical severity [86]. The question remains difficult to answer in the absence of a validated, dedicated assessment tool.

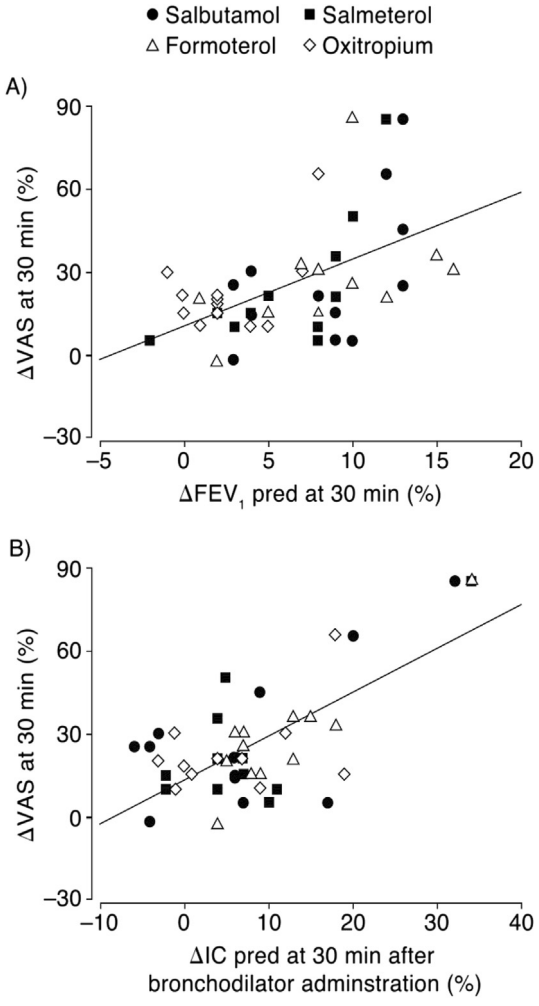

Fig. 1. Relationship of changes in dyspnea measured by visual analogue scale with placebo correction (%) with changes in (A) FEV_1 and (B) IC 30 min after bronchodilation in patients with baseline IC lower than 80% predicted. (A) $r = 0.52$; $r^2 = 0.27$; $p < 0.001$; (B) $r = 0.70$; $r^2 = 0.48$; $p < 0.001$. In patients with IC >80% predicted (not shown), the correlations were $r = 0.21$; $r^2 = 0.05$; $p = 0.26$ for FEV_1 and $r = 0.38$; $r^2 = 0.15$; $p < 0.05$ for IC. FEV_1, forced expiratory volume in 1 s; IC, inspiratory capacity; pred, predicted; r, correlation coefficient; r^2, coefficient of determination. Reproduced with permission of the European Respiratory Society [81]. © European Respiratory Society (2003).

An early (day 1) onset of effect may be useful in the context of a pulmonary rehabilitation program, where optimizing bronchodilator therapy at the outset has been recommended [87]. In COPD, exercise is limited by breathing discomfort (dyspnea) before leg discomfort (peripheral muscle fatigue) [88]. By overcoming dyspnea with a bronchodilator, the exercise program could focus on improving peripheral muscle function [87]. If the commencement of treatment coincides with the start of the exercise program, there may be a benefit for patients. Among the once-daily bronchodilators, in studies using submaximal constant load cycle ergometry testing, both LAMAs glycopyrronium and tiotropium were reported to increase exercise endurance time and exertional dyspnea when evaluated 2–3 h post-dose on the first day of treatment, with reduction in leg discomfort occurring at a later assessment [88,89]. The LABA indacaterol improved exercise endurance time but not exertional dyspnea (measured at end of exercise) after the first dose [90].

5. Benefits of sustained duration of effect

5.1. Once-daily vs twice-daily bronchodilators

In terms of standard clinical outcomes (lung function, symptoms and health status) measured in clinical studies, the once-daily bronchodilators (LAMA or LABA) have generally performed better than the twice-daily agents (LABAs), where comparisons have been performed [8,9,57,91,92] (Table 5). Of note, the 1-year POET study showed that, in patients with moderate-to-very-severe COPD, the once-daily LAMA tiotropium was more effective than the twice-daily LABA salmeterol in preventing exacerbations [93]. This finding cannot necessarily be extrapolated to other LABAs.

5.2. Comparison of once-daily bronchodilators with different onsets of action

Among the once-daily bronchodilators, tiotropium is the most commonly employed active comparator, as it was the first once-daily inhaled bronchodilator available. In several studies, bronchodilators with a fast onset have been compared with tiotropium (Table 6). As previously shown in Table 3, glycopyrronium has a faster onset of action than tiotropium. For clinical outcomes (Table 6), the two LAMAs had similar effects on symptoms, health status, rescue-medication use and exacerbations. The once-daily LABA indacaterol performed better than tiotropium for symptoms and health status [94], but tiotropium was more effective in preventing exacerbations in patients with severe or very severe airflow limitation [95] (Table 6). Indacaterol, may, therefore be more useful clinically in patients at low risk of exacerbations (the GOLD-defined patient Groups A and B), although this hypothesis requires formal testing. It should be noted that the studies summarized in the table were not necessarily designed or powered to compare the selected treatments and endpoints shown in the table.

6. Adherence/persistence

Adherence is poor in COPD, typically around 50% in practice [98–102]. Poor adherence is associated with worse clinical and economic outcomes [103–107]. Many factors are implicated [102], including the patient's understanding of the disease and their

Table 5
Once-daily (qd) vs twice-daily (bid): bronchodilation, health status and symptom-based outcomes (measured at end of study unless otherwise stated) in phase III studies of ≥12 weeks' duration.

Comparison	Bronchodilation (trough FEV_1)	Symptoms	Health status	Rescue use over study duration	Exacerbations (moderate/severe) as efficacy outcome	Ref.
Tiotropium 18 μg qd (n = 209) vs salmeterol 50 μg bid (n = 213), 24 wks	52 mL (p < 0.01)	TDI score difference 0.78 points (p < 0.05); 42% vs 35% responders (NS)	SGRQ total score difference −1.6 units (NS); 51% vs 40% responders (p < 0.05)	Change from baseline −1.45 vs −1.44 puffs/d (NS)	NR	[8]
Indacaterol 150 μg qd (n = 333) vs salmeterol 50 μg bid (n = 334), 6 mo	70 mL (p < 0.001)	TDI score 1.45 vs 0.90 (p < 0.05) (wk 12); 57–61% vs 49–54% responders[a] (wks 4–26)	−5.0 and −4.1 vs placebo; 53% and 49% responders[a]	Change from baseline −1.3 vs −1.2 puffs/d (NS)	NR	[9]
Indacaterol 150 μg qd (n = 560) vs salmeterol 50 μg bid (n = 563), 12 wks	60 mL (p < 0.001)	TDI score difference 0.63 points (p < 0.001); 69.4% vs 62.7% responders (p < 0.05)	NR	Difference −0.18 puffs/d (p < 0.05)	NR	[91]
Indacaterol 300 μg qd (n = 437) vs formoterol 12 μg bid (n = 435), 1 yr	110 mL (p ≤ 0.001)	TDI score difference 0.29 points (NS)	SGRQ score difference −0.7 units (NS)	Difference −0.34 puffs/d (p < 0.05)	0.60 vs 0.56 per year (NS); 32.8 vs 31.5% of patients (NS)	[57]
Tiotropium 18 μg qd (n = 158) vs aclidinium 400 μg bid (n = 171), 6 wks	Difference in change from baseline −38 mL (NS)	E-RS total score −0.7 (NS)	NR	Difference −0.7% rescue-free days (NS)	NR	[66]
Tiotropium 18 μg qd (n = 221) vs formoterol 12 μg bid (n = 210), 6 mo	NR	Total daily symptom score 4.50 vs 4.29 (median)[a,b]	SGRQ score differences vs placebo: −2 vs −3 units	0.67 vs 1.30 puffs/d (median)[a]	10.4 vs 8.1% of patients (moderate) (p < 0.05, formoterol vs placebo); 2.3% vs 0.5% (severe)	[92]
Tiotropium 18 μg qd (n = 3707) vs salmeterol 50 μg bid (n = 3669), 1 yr	NR	NR	NR	NR	17% reduction in risk (p < 0.001); rate ratio 0.89 (95% CI 0.83, 0.960); p = 0.002	[93]

Responders are those patients with an improvement from baseline equal to or exceeding the minimum clinically important difference (TDI ≥1 point; SGRQ ≥ −4 units). E-RS, EXAcerbations of Chronic pulmonary disease Tool (EXACT)-Respiratory Symptoms; NR, not reported; NS, not significantly different; SGRQ, St George's Respiratory Questionnaire; TDI, transition dyspnea index.
[a] Statistical comparison not reported.
[b] Total daily symptom score = sum of scores for breathlessness, cough, wheeze, amount and color of sputum, each scored on a 0–3 scale where 0 = no symptoms.

medication and inhaler [106,108–111], and frequency of dosing [98,102,112–114].

The relative simplicity and convenience of once-daily dosing (compared with multiple daily dosing) may encourage patients' adherence and persistence with their long-term medications. In one retrospective study of a claims database, adherence was strongly correlated with dosing frequency, with 43.3, 37.0, 30.2 and 23.0 percentage days covered for patient cohorts receiving once, twice, three times or four times daily treatment [112]. Similarly, in a study to determine the effect of dosing frequency of mometasone

Table 6
Selected treatment comparisons (at study endpoint) between glycopyrronium or indacaterol vs tiotropium for health status and symptom-based outcomes.

Comparison	Symptoms (TDI total score, points)	Health status (SGRQ total score, units)	Rescue use over study duration, puffs/day	Moderate/severe exacerbations, rate ratio (95% CI)	Ref.
Glycopyrronium vs tiotropium open label, 52 wks	−0.1 (NS)	−0.5 (NS)	0.3 (NS)	0.82 (0.61, 1.09) (NS)[b]	[67]
Glycopyrronium vs tiotropium blinded, 12 wks	−0.2 (NS)	0.7 (NS)	0 (NS)	1.10 (0.62, 1.93) (NS)	[96]
Glycopyrronium vs tiotropium, 26 wks	Differences from placebo: 0.9 vs 0.6 (NS)	Differences from placebo: −1.8 vs −0.9 (NS)	Differences from placebo: −0.3 vs −0.4 (NS)	N/A	[10]
Glycopyrronium vs tiotropium, 62 wks[a]	N/A	−0.6 (NS)[b]	N/A	1.03 (0.91, 1.16) (NS)\	[97]
Indacaterol 150 μg and 300 μg vs tiotropium 18 μg od (open label), 26 wks	Differences from placebo: 1.0 and 1.2 vs 0.9 (NS)	Differences from placebo: −3.3* and −2.4 vs −1.0 (*p < 0.05 vs tiotropium; NS for 300 μg)	Changes from baseline: −1.5* and −1.6* vs −1.0 (*p < 0.05 vs tiotropium; NS for 300 μg)	0.96 (0.64,1.43) and 1.06 (0.71,1.57) (NS)[b]	[60]
Indacaterol 150 μg vs tiotropium 18 μg od (blinded), 12 wks	0.6 (p < 0.001)	−2.1 (p < 0.001)	−0.5 (p < 0.001)	N/A	[94]
Indacaterol 150 μg vs tiotropium (blinded), 52 wks[a]	0.3 (p = 0.02)	0.2 (NS)	−0.6 (p < 0.001)	1.24 (p < 0.001)	[95]

N/A = not applicable (not analyzed or not reported); NS = not significant; TDI = transition dyspnea index; SGRQ = St George's Respiratory Questionnaire.
[a] Study conducted among patients with severe or very severe COPD.
[b] Unpublished data (supplied by study sponsors on request).

on treatment adherence in patients with asthma, mean adherence rates were greater with a once-daily regimen compared with twice daily [115]. In a survey of patients with COPD, those who reported low adherence were more likely to prefer once-daily medication than were those with good adherence; this preference was found to be associated with a high self-perceived need for controller medication [116], indicating the importance of tailoring treatment decisions to the individual patient's needs and preferences. Persistence with inhaled medications for COPD is also directly related to the daily frequency of administration [117].

A fast onset may also be useful in the case of missed doses, a form of non-adherence that is common in COPD [118,101]. Adherence is reported to be lower for medications that do not have an immediate effect on symptoms [102].

7. Remaining questions and future research

It is still not firmly established whether long-acting bronchodilators should be started in obstructed patients in the absence of symptoms, and whether it is better to start with a β_2-adrenergic agonist or an antimuscarinic agent in patients with mild/moderate stable COPD. Thus, in almost all guidelines, no distinction is made as to which class of bronchodilators should be considered first; rather, they only recommend the use of long-acting agents. Similarly, the guidelines do not advise on whether once-daily or twice-daily dosing is preferable, although the weight of evidence supports the better clinical efficacy of the once-daily agents. Moreover, although LABA/LAMA combinations are recommended as an option for patients with increased symptoms and for those at higher risk of exacerbations [1], there is currently no real guidance on when such treatments should be applied in preference to alternative treatments [119]. In any case, it is likely that the lack of indication of bronchodilators class that should be used as first choice is due to the fact that the putative superiority of one class over another documented by some randomized clinical trials was based on only one specific outcome or method of research, the results of which might not be generalizable [119].

Given the many different variables affecting adherence, it is probably an oversimplification to suppose that using a highly efficacious treatment will in itself lead to improved adherence. Indeed, in the TORCH study, the association between increased adherence and improved mortality and reduction in hospital admission was independent of study treatment. The effect of treatment was more pronounced in patients with good adherence than in those with poor adherence, rather than adherence being better in patients receiving the most effective treatment [103].

The relationship between a simple dosing regimen and improved adherence has been reasonably well studied in asthma and COPD [115,116,120], and using a medication dosed once daily should help in addressing the problem of non-adherence. A patient's perception of benefit when restarting a medication or changing to a faster-onset one may be useful to the treating physician in improving the management of a poorly adherent patient. However, further research is warranted to explore the association between a fast onset and adherence, especially in terms of how best to measure fast onset, e.g. patients' perception, subjective experience and clinical effect. Many of these concepts are not easily investigated within the constraints of a randomized, controlled trial, and a more pragmatic approach using observational research will be required.

There are also challenges in terms of how best to define and measure adherence. Research techniques to address adherence with inhaled medication include canister weighing and electronic monitoring of inhaler actuation. Self-reporting is a simple and easy way to assess adherence and is useful in identifying patients' reasons for non-adherence [121], although the accuracy of this method has been questioned [122]. Numbers of filled prescriptions are used as an indicator of adherence/persistence, but again may not reflect medications taken. Inhalers can now be fitted with electronic monitoring devices that can allow clinicians to track adherence and/or trigger reminders of missed doses direct to the patient. This type of monitoring could help identify barriers to adherence and provide a basis for subsequent discussions with non-adherent patients [123].

In 2008, Bourbeau & Bartlett identified a need to develop effective treatments for COPD with simplified treatment regimens (infrequent dosing, simple delivery), rapid onset of action and durable effect, which would increase the probability of patient adherence [102]. Among the various effective agents available to prescribers today, choosing a once-daily bronchodilator with a fast onset of action (or combination thereof) provides an ideal pharmacodynamic profile that may encourage patient adherence. Use of combination inhalers may improve adherence if it reduces the daily number of medications [101]. Effecting a behavioral change in non-adherent patients requires patient-centered care characterized by concordance (i.e. shared decision-making about therapy by doctors and patients). Effort should be focused on patient education regarding the importance of regular administration and exploring patients' perceptions of their burden of therapy and their goals and expectations from COPD treatment.

Disclosures

In the past 3 years, MC has received fees for speaking, organizing education or consulting from Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Guidotti, Lallemand, Malesci, Mundipharma, Novartis, Pfizer, Veronapharma, and Zambon, and research funds from Almirall, Novartis and Veronapharma.

The institution where KMB is employed has received compensation for organizing or participating in advisory boards for Almirall Hermal, Cytos, Chiesi, Boehringer Ingelheim, AstraZeneca, Mundipharma, Novartis, and Revotar Biopharmaceuticals, and participation in scientific meetings or courses supported by various pharmaceutical companies (Almirall Hermal, AstraZeneca, Boehringer Ingelheim, Novartis, Pfizer, and Takeda) in the past 3 years. KMB's institution has also received consulting fees from Ablynx, Apellis Pharmaceuticals, Chiesi, and Cytos. The institution has received compensations for the design, performance or participation in single or multicenter clinical trials in the past 3 years from several companies including Almirall, Boehringer Ingelheim, Cytos, GSK, Mundipharma, Novartis, Pfizer, Revotar Biopharmaceuticals, Sterna AG, and Teva.

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