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Pharmacological mechanisms leading to synergy in fixed-dose dual bronchodilator therapy

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Long-acting β_2 adrenoceptor agonists (LABAs) in combination with long-acting muscarinic antagonists (LAMAs) can elicit functional and clinical benefits in chronic obstructive pulmonary disease (COPD). LABA/LAMA combinations synergistically relax human isolated airways at the level of the medium and small bronchi. LABAs and LAMAs both modulate the bronchial tone via different pathways localized at the level of presynaptic parasympathetic fibers and airway smooth muscle cells. The exact nature of the interactions between these pathways is not completely understood, but there is cross-talk at many levels in airway smooth muscle cells that is also regulated by the activity of calcium-activated potassium channels and protein tyrosine kinases. While the synergy between LABAs and LAMAs is a class effect, some of the currently available fixed-dose combinations (FDCs) do not induce synergistic interaction because the individual components are not appropriately balanced in the combination. Concerns remain on the cardiovascular safety profile of LABA/LAMA FDCs.

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Introduction

Dual combination therapy is the cornerstone for the treatment of patients with chronic obstructive pulmonary disease (COPD) [1]. The last international recommendations for the pharmacological treatment of COPD, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) strategy, suggest combining a long-acting β_2 adrenoceptor (β_2-AR) agonist (LABA) with a long-acting muscarinic antagonist (LAMA) in most COPD patients, namely highly symptomatic patients with $\leq$1 moderate exacerbation in the previous year (GOLD group B), patients with mild symptoms and $\geq$2 moderate or $\geq$1 severe exacerbations in the previous year (GOLD group C), and highly symptomatic patients with $\geq$2 moderate or $\geq$1 severe exacerbations in the previous year (GOLD group D) [1].

LABAs prevalently activate β_2-ARs, although they have also some activity at the level of β_1-ARs. LAMAs are characterized by kinetic selectivity for the M_3 muscarinic acetylcholine receptor (mAChR), as the dissociation rate from this receptor is slower that from other mAChRs localized in the airways, namely M_1 and M_2 mAChRs [2–4]. Detailed pharmacological characteristics of the LABAs and LAMAs included in the currently approved fixed-dose combinations (FDCs) are reported in Table 1. The bronchorelaxant effect of long-acting bronchodilator agents depends by the time necessary to reach the their pharmacokinetic steady state, that for LABAs and LAMAs may take up to 3 weeks. However, the differences in bronchodilation between first dose and steady state may also depend by the level of accumulation of the drugs in the airways during this time, and the pharmacokinetic/pharmacodynamic characteristics of each single agent. The duration of action and the dosing frequency (i.e. once-daily or twice-daily) are not the same for all the LABAs and LAMAs, since they are correlated with the maintenance dose and the pharmacological characteristics of each specific bronchodilator agent [2].

LABA/LAMA combinations elicit bronchorelaxant effects by acting on two of the main mechanisms that regulate the airway smooth muscle (ASM) tone. Specifically, LABAs stimulate the sympathetic pathway whereas LAMAs inhibit the parasympathetic pathway, thus leading to intense and sustained bronchorelaxant effect [4]. Overall, dual bronchodilation therapy leads to unquestionable clinical benefits compared with monocomponents by improving lung function, quality of life, exercise tolerance, and reducing dyspnea and the risk of exacerbations of COPD [5,6,7•,8].

The combination of two drugs characterized by different mechanisms of actions may lead to three main conditions: additive effect, synergy (an effect that is more than additive) and antagonism (an effect that is less than additive). Obviously, the toxicities of the drugs in the host should not overlap [9••]. Thus, the rationale for dual combination therapy in COPD should be to elicit

Table 1

Synthesis of the main pharmacological characteristics of LABAs and LAMAs included in the currently approved FDCs with regard to human β-ARs and mAChRs

	Drugs	Main pharmacological targets				Secondary targets	Functional selectivity	References
		β_2-AR				β_1-AR	β_2/β_1 ratio	
		pKi	IA (% isoprenaline)	Onset of action ($t_{1/2}$, min)	Duration of action (h)	pKi		
LABAs	Formoterol	8.06	95.0	5.9	0.93	6.10	130	[3,36–40]
	Indacaterol	7.64	86.0	10.9	9.75	6.21	12.5	[3,36–38,40]
	Olodaterol	9.14	88	NA	NA	7.33	65	[3,39]
	Vilanterol	9.42	70.00	3.45	NA	NA	2400	[3,36]

		M_3 mAChR				M_1 mAChR		M_2 mAChR		M_3/M_2 ratio	
		pKi	K_{off} (h^{-1})	Onset of action ($t_{1/2}$, min)	Duration of action (h)	pKi	K_{off} (h^{-1})	pKi	K_{off} (h^{-1})		
LAMAs	Aclidinium	9.85	0.071	8.20	10.7	10.0	NA	9.85	0.39	5.9	[2,41–44]
	Glycopyrronium	9.28	0.11	8.72	6.1	9.77	NA	9.09	1.84	16.5	[2,41–43,45]
	Tiotropium	9.72	0.091	10.2	27	10.05	NA	9.82	0.79	8.7	[2,41–43,45]
	Umeclidinium	9.80	0.53	9.0	1.37	9.80	NA	9.82	4.44	8.7	[2,43,46]

β-AR: β adrenoceptor; FDCs: fixed-dose combinations; IA: intrinsic activity; K_{off}: dissociation rate; LABAs: long-acting β_2 adrenoceptor agonists; LAMA: long-acting muscarinic antagonists; mAChR: muscarinic acetylcholine receptor; NA: not available in human tissue; pKi: the negative logarithm to base 10 of the equilibrium dissociation constant of a ligand determined in inhibition studies; $t_{1/2}$: residence half-life.

synergism in therapeutic efficacy, diminish the risk of adverse events (AEs), and reduce the doses required for a given effect.

Overall, the key assumption to assess whether a combination therapy induces synergistic or antagonistic interaction with regard to a certain outcome is to quantify the additive effect [10]. The focus of this review is to illustrate how dual bronchodilation therapy may optimize the synergistic interaction between LABAs and LAMAs in COPD.

Pharmacological modeling of drug interaction

Several research groups have spent decades identifying an appropriate framework for studying drug interactions. To date, however, there is no consensus on a single model that permits the adequate and objective quantification of an additive effect [9••].

Nevertheless, at least in the field of respiratory pharmacology, two methods have been identified to be suitable to identify the additive effect in both *in vitro* experimental settings and/or in clinical trials, namely the *Bliss Independence criterion* and the *Unified Theory* [10].

The *Bliss Independence model* is based on the assumption that different agents act independently of each other in terms of their mode and the site of action. The basis of the Bliss Independence model is represented in the equation:

$$E(x,y) = Ex + Ey - (Ex * Ey)$$

where E is the fractional effect (between 0 and1), and x and y are the doses (or concentrations) of drugs in the combination. Observed effects greater or smaller that $E(x, y)$ indicate synergism or antagonism interaction, respectively [11]. The Bliss Independence theory provides the statistical significance of drug interaction and can be easily applied to both *in vitro* experiments and clinical trials since the equation works even with data from single combination points [10,12].

The *Unified Theory* is based on the concept of Combination Index, which results from the synthesis of four major biochemical and biophysical models (the Henderson–Hasselbalch, Hill, Michaelis–Menten, and Scatchard equations) [9••]. The basis of the *Unified Theory* is represented in the following equation:

$$CI = \frac{(D_{n\%})_{xy}}{(D_{n\%})_x} + \frac{(D_{n\%})_{xy}}{(D_{n\%})_y}$$

where CI is the Combination Index, D is the dose (or concentration), $n\%$ is the percentage of effect, x and y are the tested drugs administered alone or in combination (xy). CI < 1, =1, and >1 indicate synergism, additive effect, and antagonism, respectively. The Unified Theory provides the rank of drug interaction but does not allow a statistical analysis to be performed. Furthermore, unlike the Bliss Independence approach, the *Unified Theory* is more suitable for *in vitro* experiments than clinical trials