www.brn.cat

PERMANYER

BRN Rev. 2023;9(2):79-94

BRN Reviews

REVIEW ARTICLE

Inhaled Treatments for Bronchial Asthma: Molecules and Devices

Daniel R. Monserrate, MD

Pulmonary Service, Hospital de Sabadell, Institut Universitari Parc Taulí-UAB, Sabadell, Spain

ABSTRACT

Inhaled treatments for asthma involve the use of medications that are delivered directly to the lungs through inhalation. There are three family types of inhaled medications: muscarinic antagonists and β2 agonists, which are bronchodilators, and inhaled corticosteroids, which are anti-inflammatory drugs. Each of them has short- and long-acting molecules and can be found in monotherapy, double-fixed and triple-fixed combinations.
There are several types of inhalation devices available to deliver these medications and combinations: metered-dose inhalers (MDIs), dry powder inhalers (DPIs), and nebulizers. Each device has its advantages and disadvantages. MDIs are the most commonly used inhalation devices and require a proper inhalation technique to ensure the medication reaches the lungs. DPIs do not require coordination between inhalation and actuation and are easy to use but may not be suitable for all patients. Nebulizers are generally reserved for patients who have difficulty using MDIs or DPIs and will not be discussed in this article.

Keywords: Anticholinergics. Asthma. β2 agonist. Dry-powder inhaler. Inhaled corticosteroid. Metered-dose inhalers.

Correspondence to:
Daniel R. Monserrate
E-mail: drmonserrate@tauli.cat

Received: 24-07-2023
Accepted: 25-07-2023
DOI: 10.23866/BRNRev:2023-M0092
www.brnreviews.com

INTRODUCTION

Bronchial asthma is a chronic respiratory disease affecting millions of people worldwide[1]. Inhaled treatments, such as inhaled corticosteroids (ICS), long-acting beta-agonists (LABA), and long-acting muscarinic antagonists (LAMA), are widely used to manage asthma symptoms and improve patients' quality of life. However, the effectiveness of these treatments depends on several factors, including the type of inhaler device used, patient adherence, and proper technique. This article will provide an overview of the different inhaled treatments approved and available for asthma and their associated inhaler devices, highlighting their benefits and drawbacks. A summary of all the information written in the manuscript is shown in table 1 and figure 1.

MOLECULES

Inhaled medications are the cornerstone of asthma treatment and have several advantages over systemic medications. First, inhaled medications provide a more direct and targeted effect on the airways, resulting in rapid

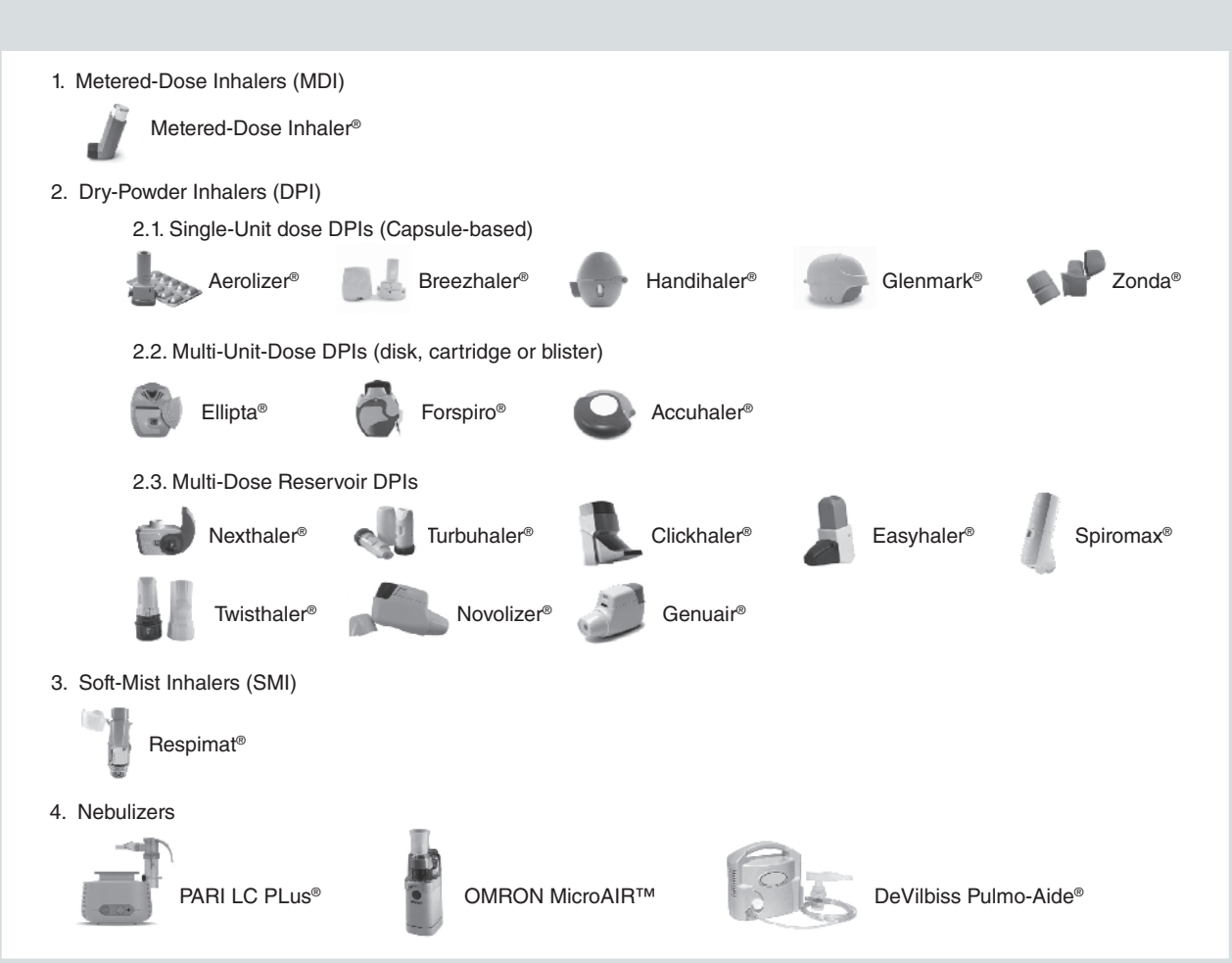

Figure 1. Different devices available in the market *(adapted from https://medicaments.gencat.cat/ca/ciutadania/tractaments/inhaladors/index.html).*

Table 1. Different drugs available in the market

Drug Class	Duration	Molecule or combination	Brand name	Dosage form	On-set of action	Dosing
SABA	6 h	Salbutamol	Ventolin – Ventoaldo Salbutamol – Butosol – Salbutamol Clickhaler DPI	MDI 100 µg/inh DPI 95 µg/inh	40-50''	200 mcg/4-6h
			Ventilastin	Novolizer 100µg/inh		
		Terbutaline	Terbasmin	TH 500 µg/inh	40-50''	500 mcg/4-6 h
SAMA	4-6 h	Ipratropium Bromide	Atrovent Atroaldo Ipratropi CIPLA	MDI 20 µg/inh	15-30 min	20-40 mcg/4-6 h
LABA	12 h	Salmeterol	Serevent; Inaspir; Beglan; Betamican; Soltel CIPLA	MDI 25 µg/inh AC 50 µg/inh	20 min	50 mcg/12 h
		Formoterol	Broncoral (AL) Broncoral Neo (PCI)	AL 12 µg/inh MDI 12 µg/inh NV 12 µg/inh TH 4.5-9 µg/inh	1-3 min	4.5-12 mcg/12 h
			Foradil (AL) – F. Neo (PCIP)			
			Formatris Novolizer			
			Oxis (Turbuhaler)			
			Formoterol – Neblik (AL)			
	24 h	Indacaterol	No monotherapy	BH 150 o 300 µg/inh	1-3 min	1 inh/24 h
		Vilanterol	No monotherapy	–	3-5 min	–
LAMA	24 h	Tiotropium	Spiriva Respimat	Respimat 2.5 µg/inh	30 min	RS 2.5 µg (2 inh)/24 h
		Glycopyrronium	No monotherapy	BH 44 µg/inh	5 min	1 inh/24 h

					Low dose (mcg/day)	Medium dose (mcg/day)	High dose (mcg/day)
ICS	12 h	Budesonide	Budesonide (EH) (MDI)	EH 100-200-400 µg MDI 50-200 µg AL-NV 200-400 µg TH 100-200-400 µg	200-400	401-800	801-1600
			Miflonide (AL – Breezhaler)				
			Pulmicort (TH)				
			Novopulm (Novolizer)				
		Beclomethasone	Beclo-Asma Becotide Becloforte Soprobec	MDI 50 -250 µg/inh MDI 250 µg/inh MDI 50-100-200-250	200-500	501-1000	1001-2000
		Fluticasone Propionate	Flixotide – Flusonal – Inalacor – Trialone – Fluticasone CIPLA	MDI 50-125-250 µg AC 100-250-500 µg CIPLA 125-250 µg	100-250	251-500	501-1000
		Mometasone	Asmanex Twisthaler	TW 200-400 µg/inh	200-400	401-800	801-1200
	24 h	Ciclesonide	Alvesco	MDI 160 µg/inh	80-160	161-320	321-1280
SABA+ ICS	12 h	Salbutamol + Beclomethasone	Ventoduo	MDI 100/50 µg	40-50''	2 inh/12-24 h to 2 inh/6 h	

Table 1. Different drugs available in the market *(Continuation)*

					Low dose (mcg/day)	Medium dose (mcg/day)	High dose (mcg/day)
ICS + LABA	12 h	Salmeterol + Fluticasone Propionate	Seretide – Plusvent Inaladuo – Anasma – CIPLA MDI	MDI 25/50-125-250 AC 50/100-250-500	20 min	1 inh/12 h 2 inh/12 h	
			Seffalair – Bropair	SX 12/100-200	15 min	1inh/12 h	
			Flusamix Easyhaler	EH 50/500	20 min	1inh/12 h	
			Inhalok Airmaster (DPI)	DPI 50/250-500	20 min	1inh/12 h	
		Formoterol + Budesonide	Symbicort – Rilast (TH and MDI) – CIPLA	4.5/80 (TH) 4.5/160 µg (ALL) Forte 9/320 µg (except MDI)	1-3 min	1 inh/12 h 2 inh/12 h (MDI) SMART therapy	
			Duoresp – Biresp (SX)				
			Bufomix – Gibiter (EH)				
			Cipla Airflusal	4.5/160 I 9/320 µg			
		Formoterol + Fluticasone	Flutiform	MDI 5/50 - 125 µg MDI 10/250 µg	1-3 min	2 inh/12 h	
		Formoterol + Beclomehtasone	Foster – Formodual	Modulite MDI/NH 6/100-200µg	1-3 min	1 inh/12 h 2 inh/12 h MART therapy	
	24 h	Vilanterol + Fluticasone Furoate	Relvar – Revinty Ellipta	22/92 µg 22/184 µg	6 min	1 inh/24h	
		Indacaterol + Mometasone	Atectura – Bemrist Breezhaler (BH)	125/62.5 125/127.5 125/260	15 min - 1 h	1 inh/24h	
ICS+LAMA+ LABA	12 h	Beclometh + Glyco + Formo	Trimbow – Trydonis MDI/Nexthaler	NH 87/9/5 µg MDI 87/9/5 µg MDI 172/9/5 µg	1-3 min	2inh/12 h	
	24 h	Mometasone + Glyco + Indac	Enerzair – Zimbus	BH 160/63/150 µg	5 min	1inh/24h	

AC: Accuhaler; AL: Aerolizer; AM: airmaster; BH: Breezhaler; DPI: dry powder inhaler; EH: EasyHaler; EL: Ellipta; GN: Genuair; HH: Handihaler; ICS: inhaled corticosteroids; LABA: long-acting beta-2 agonist; LAMA: long-acting muscarinic antagonist; MDI: metered-dose inhaler; NH: Nexthaler; NV: Novolizer; RS: Respimat; SABA: short-acting beta-2 agonist; SAMA: short-acting muscarinic antagonist; SX: Spiromax; TH: Turbuhaler; TW: Twisthaler.

relief of symptoms and improved lung function. Second, inhaled medications have fewer side effects compared to systemic medications, as they are delivered directly to the lungs, thereby reducing the risk of systemic side effects[2], such as weight gain, osteoporosis, and adrenal suppression. Third, inhaled medications are convenient to use and can be easily self-administered by patients, resulting in improved adherence to treatment.

Clinical indications

These treatments can be used as rescue or maintenance treatment[1]. Rescue treatment, also known as quick-relief or short-acting medication, is used to provide immediate relief of symptoms during an asthma attack or when symptoms occur unexpectedly. Maintenance treatment, also known as long-term or controller medication, is used to prevent or

reduce the frequency and severity of asthma symptoms over time. These medications work by reducing inflammation and swelling in the airways, which can lead to fewer asthma attacks and better overall control of the condition. It is important to note that rescue treatment should not be used as a substitute for maintenance treatment.

Characteristics of the molecules marketed for asthma: the ABC rule

There are different classes of inhaled molecules; the most recommended according to international guidelines are bronchodilators[3] and corticosteroids. The list is large and difficult to memorize. An easy way to remember the three families of inhaled medications available so far to treat asthma is to remember the "ABC rule" of inhaled treatment:

- A: Anticholinergics (also named Muscarinic antagonist)
- B: β2-agonists
- C: Corticosteroids

We will below discuss their characteristics.

Anticholinergic or muscarinic antagonist

Parasympathetic neuronal activity, through acetylcholine signaling, is increased in the pathophysiology of asthma. Acetylcholine is a neurotransmitter that favours bronchoconstriction, mucus secretion and contributes to airway inflammation[4,5]. There is also some evidence suggesting its involvement in airway remodeling[6].

Blocking acetylcholine can help to relax the muscles around the airways, thus improving airflow, decreasing inflammation, and inhibiting secretion and clearance of mucus[7].

Acetylcholine binds to airway muscarinic receptors: M1, M2 and M3[8]

- M1 receptors are expressed by epithelial cells and in the ganglia. They regulate electrolyte and water secretion, and aid parasympathetic neurotransmission respectively.
- M2 receptors are expressed in airway smooth muscle, cardiac tissue and on parasympathetic neurons. Even though they have a very limited role in airway contraction, they act as autoreceptors on parasympathetic neurons to limit acetylcholine release, thus limiting vagal reflex-induced bronchoconstriction and mucus secretion.
- M3 receptors are the primary receptor subtype for bronchial smooth muscle contraction. They are found in airway smooth muscle and submucosal glands.

Muscarinic antagonists used in asthma are reversible competitive inhibitors of M1, M2 and mainly M3 receptors. The time spent at the muscarinic receptors determines the duration of action of each drug.

There are five anticholinergic molecules, all currently licensed for use in chronic obstructive pulmonary disease (COPD), but only three molecules are approved for asthma treatment:

– One short-acting muscarinic antagonist (SAMA): ipratropium bromide, typically used in combination with short-acting β2-agonists (SABAs) or ICS to provide additional bronchodilation and improve lung function. It can be used as an alternative reliever agent for patients with asthma refractory to β2-agonists.

– Two LAMAs:

  • In 2015, Tiotropium Bromide Respimat® 5µg was approved for asthma[9] as add-on therapy to ICS and a LABA. There is extensive evidence showing an improvement in lung function, risk reduction for severe asthma exacerbation and improved asthma control.

  • Recently in 2020, Glycopyrronium bromide was approved only in triple-fixed combination with indacaterol and mometasone[10] (see fixed-combinations below).

Umeclidinium is licensed for use in COPD, but Phase II and Phase III clinical trials are ongoing to obtain the indication in asthma. Aclidinium, at the time of writing, has no clinical trials in asthma.

Anticholinergics have a different mechanism of action compared to β2-agonist[11]. However, data suggest concomitant use of both molecules can enhance the β2-agonist-induced bronchodilation via intracellular processes. The so-called "dual bronchodilation" has a greater benefit than single bronchodilation. Properly, we should call it the bronchodilation + bronchoconstriction inhibition effect since this is the effect of antimuscarinic drugs.

β2-AGONISTS

β2-agonists work by binding to β2 adrenergic receptors in the lungs, mimicking the effects of adrenaline, which leads to relaxation of the smooth muscles[12,13].

The β-receptor is a glycoprotein embedded in the plasma membranes of a number of cell types. Three distinct subtypes of β-receptors are known: β1; β2; β3; found predominately in cardiac muscle, airway smooth muscle and adipose tissue, respectively[14].

Approximately 80% of the β-receptors in the lungs are of the β2-subtype. However, there is a homology of 54% between the human β1- and β2-subtypes, which may result in any highly selective β2-agonist affecting β1-receptors.

90% of the β2-receptors in the lungs are thought to be located in the alveolar wall, with the remainder found on smooth muscle cells and in the membranes of epithelial, endothelial and mast cells. Smooth muscle cells may each contain 30.000–40.000 β2-receptors[15].

β-receptor activation increases levels of intracellular cyclic adenosine monophosphate (cAMP) via G-protein activation of adenyl cyclase. The cAMP is then thought to influence key regulatory proteins involved in the control of muscle tone, inhibit calcium ion release from intracellular stores, reduce calcium ion entry into the cells, and sequester intracellular calcium ions[16]. The result is a relaxation of the central and peripheral airway smooth muscle and hence bronchodilation.

The total effect of any β2-agonist involved in bronchodilation is a property of its β2-receptor

binding affinity and its ability to induce an intracellular response. The latter is due to a conformational change in the receptor leading, in turn, to one or more intracellular events[12].

There are three main types of β2-agonists used in asthma treatment:

– SABAs
  Widely used, with effective bronchodilation occurring within two-three minutes and peak bronchodilation within 15 minutes of inhalation. However, they have a short duration of action, which does not exceed four-six hours. Thus, they are used for quick relief of asthma symptoms (wheezing, coughing and shortness of breath).

  - Salbutamol
  - Terbutaline

– LABAs
  Molecules developed to interact specifically with the β2-receptor, with a 12h duration of action.

  - Formoterol: has a β2-receptor selectivity, with a fast onset of bronchodilation (within 1-3min, acting rapidly like salbutamol) and a prolonged effect that can last up to 12h.

  - Salmeterol: is a partial agonist at the β2-receptor, has a slower onset of bronchodilation (30 min) although it has a long-lasting effect (12 hours).

– Ultra-LABAs[17]
  The term was coined in 2005 to indicate once-daily β2-receptor agonists. All have a near full-agonist profile at the human β2-receptor. Only two molecules are approved for asthma treatment in combination with ICS:

  - Indacaterol
  - Vilanterol

Corticosteroids

ICS, also known as glucocorticoids, are now first-line therapy for all patients with persistent asthma, controlling asthma symptoms and preventing exacerbations[18]. Through inhalation, the drug is delivered directly to the lung, minimizing the systemic side effects associated with oral or parenteral administration.

They suppress inflammation mainly by switching off multiple activated inflammatory genes, reducing airway hyperresponsiveness and controlling asthma symptoms.

When comparing different ICS medications for asthma management, there are several factors to consider, including their efficacy, safety, side effects, and cost.

The differences in the pharmacokinetic (PK) characteristics of ICSs influence the profile of each of them, but also the significant differences in glucocorticoid receptor (GR) selectivity, potency and physicochemical properties (lipophilicity, solubility) are critical in defining the pharmacodynamics (PD) profile of an ICS[19].

To determine the efficacy and safety of ICSs, it is essential that the dose, oral and pulmonary bioavailability, clearance and distribution volume, ability to bind to GR and to secondary produce a response.

ICSs are absorbed from the lung and gut (approximately 50% of inhaled drugs may be swallowed) being responsible for the systemic bioavailability and having the potential to induce systemic adverse effects by interacting with systemic GR. However, the risk of systemic adverse effects from an ICS depends considerably upon its dose and potency, the delivery system, systemic bioavailability, first-pass hepatic metabolism and half-life of the fraction of the drug in the systemic circulation[20].

ICSs pass the phospholipid double layer of pulmonary cell membranes and link to the GR widely expressed in most cell types. There are two different types of GRs:

– Type I or mineralocorticoid receptor

– Type II or glucocorticosteroid receptor, where all ICS bind to.

– Type II also has two human isoforms:

  • GRα, which mediates most of the known glucocorticoid actions (see below)

  • GRβ, originated from the same gene, remains in the nucleus, and does not act on ICS. It can actually act as a dominant negative inhibitor and antagonizes GRα activity. High levels are linked with glucocorticoid resistance.

GRα remains in the cytoplasm as part of a large multiprotein complex. When corticosteroid binds to the receptor, the ligand-glucocorticoid complex becomes hyperphosphorylated, dissociates from the multiprotein complex and migrates towards the nucleus, where it binds to DNA sequences called GR response elements. The resulting complex acts as an activator or repressor of proteins that initiate the transcription of some genes by RNA polymerase II. The ligand-glucocorticoid complex also interacts with other transcription factors such as NF-κB or AP-1, which elicit the synthesis of different proinflammatory cytokines. Finally, GR also switches off multiple activated inflammatory genes through reversing histone acetylation via the recruitment of histone deacetylase 2 (HDAC2).

The ICS approved for asthma treatment in Europe include:

– Fluticasone propionate (FP)

– Fluticasone furoate (FF)

– Budesonide (BUD)

– Beclomethasone dipropionate (BD)

– Mometasone furoate (MF)

– Ciclesonide (CIC)

– Triamcinolone acetonide (TAA)

The only PD parameter that varies between different ICSs is the GR binding affinity, which is usually given in comparison with an affinity of 100 for the standard dexamethasone (and all ICSs have greater affinity than dexamethasone).

The higher affinity to GR, the more potent the ICS. Generally, the greater anti-inflammatory activity, the greater efficacy, but also the greater occurrence of systemic side effects. However, some molecules have high binding affinity but without efficacy due to other PK and PD factors.

The therapeutic index of any ICS, which is the ratio between pulmonary activity and systemic activity, is enhanced when an ICS is slowly absorbed from the lung tissue and presents a rapid systemic clearance. The pulmonary efficacy is maximized by high lung deposition, high receptor binding, long pulmonary residence times and high lipid conjugation. Nevertheless, since the pharmacological activity of a drug depends on its free concentration at the receptor site, it is likely that ICSs with a high plasma and tissue binding can reduce systemic side effects but also show less therapeutic efficacy in the lungs compared to ICSs with weak plasma and tissue binding, when administered in a similar microgram dose, because they would provide lower pharmacologically appropriate concentrations in the lungs[21].

There is a paucity of studies assessing systemic adverse effects associated with ICS use in asthma. Those studies that have been carried out present conflicting findings and are limited by multiple biases and residual confounding[22].

The incidence of local side-effects commonly associated with ICS, such as oropharyngeal candidiasis, dysphonia, reflex cough, bronchospasm and pharyngitis, can be variable and depend on both the type and dose of ICS used and the mode of delivery (metered-dose inhaler [MDI] or dry-powder inhaler [DPI])[23,24].

Fixed combinations

In asthma, inhaled β_2-agonists and corticosteroids are frequently used together in the control of asthma and it is now recognized that there are important molecular interactions between these two types of drugs[25].

The most frequent combinations are ICS + LABA:

- Any ICS (except Ciclesonide) ranging low, medium and high dose.
- 12-hour duration LABA: Formoterol, Salmeterol
- 24-hour duration LABA: Vilanterol and ultimately Indacaterol.

There is still an ICS + SABA combination available: Beclomethasone + Salbutamol.

Finally, two triple fixed-dose combinations are approved for asthma (ICS+LABA+LAMA)[26-29]:

- 24-hour duration: Mometasone/Indacaterol/Glycopyrronium
- 12-hour duration: Beclomethasone/Formoterol/Glycopyrronium

These triple fixed-dose combinations are typically prescribed for adults with moderate-to-severe asthma who require additional control despite treatment with ICS/LABA combination therapy.

DEVICES

As we have seen so far, the different molecules and drugs used to treat asthma involve the use of inhaled medication, which is delivered directly to the lungs, thus reaching better local effects and preventing systemic side effects.

The effectiveness of these treatments depends on several factors, among which the type of inhaler device used, patient's adherence, and proper technique.

There are several types of inhalation devices available to deliver these medications and combinations:

– MDIs

– DPIs

– Soft-mist inhalers (SMIs)

– Nebulizers.

Metered-dose inhalers (MDIs)

MDIs are the most commonly used inhaler devices for asthma. They consist of a pressurized canister that contains medication in a liquid form, and a metering valve that delivers a precise amount of medication with each inhalation. The canister is inserted into a plastic holder with a mouthpiece.

When the patient inhales through the mouthpiece, a spray of medication is released from the canister and into the lungs.

MDIs require coordination between pressing the canister and inhaling the medication, which can be difficult for some patients, especially children, the elderly, and those with severe asthma.

MDIs have a higher carbon footprint compared with other devices, due to the global warming potential of the propellant gas they contain (originally chlorofluorocarbon (CFC), later replaced with hydrofluorocarbon), which aerosolizes the drug formulation to produce a high-velocity spray[30].

The use of propellants and the production of the high-velocity spray mean that inhalation from MDIs must be well timed and well controlled (slow and steady), otherwise the spray may be deposited largely in the mouth or throat[31].

Even with the right inhalation technique, MDIs can leave a high deposition of the drug in the patient's mouth and oropharynx. Spacers and valved holding chambers (VHCs) can help to alleviate the difficulty of inhaling while pressing for users of MDIs[32-34].

A spacer is a tube or extension device that is placed at the interface between the patient and the MDI. VHCs have a one-way valve at the mouthpiece end to allow inhalation and prevent exhalation into the chamber. VHC Spacers and VHCs enable the patient to breathe from a "standing aerosol cloud" that does not require breath coordination. These inhalation aids reduce the speed of the emitted aerosol and allow for the evaporation of propellant from larger droplets reducing oropharyngeal deposition and increasing deep lung deposition. With Spacers, the inspiratory effort of the patient is not as critical, they can use tidal breathing if the spacer has a valve, and therefore they are likely to receive a higher lung deposition than when using an MDI alone. It is also preferable to use during acute exacerbations[35].

However, spacers can also reduce the doses delivered from MDI due to electrostatic

precipitation. They are less portable, bring additional cost, require the correct maintenance and patients have to remember that they must discharge only one dose into the chamber before an inhalation.

Initial MDIs did not have dose counter, which meant additional difficulties for patients in determining when the MDI should be replaced. Fortunately, new devices have appeared with integrated dose counter, allowing a better control and adherence to the therapy[36].

Types of MDIs available for asthma treatment

– Conventional MDIs: these were the first MDI devices, most commonly used. They have chlorofluorocarbon (CFC) propellant and medication in a pressurized canister, a metering valve and a plastic holder with a mouthpiece.

– Modulite®: It may seem like a conventional MDI, but it has many improved features. It is the first device with CFC-free solution formulations[37], based on the propellant hydrofluoroalkane (HFA)-134a[38]. The design allows the size and distribution of particles to be tailored, due to the quantity of co-solvent, the actuator orifice geometry, the non-volatile components of a solution formula, the volume of the metered solution and the vapor pressure of the propellant.

  Enabling drug delivery to be targeted to different parts of the lung has led to the development of the 'superfine' particle HFA solution systems, which allow for deeper penetration into the smaller airways of the lungs. A superfine formulation is defined as having a mixture of ultrafine (diameter < 100 nm) and extra-fine (diameter ≤ 1 mm) particles[38,39].

– Breath-Actuated Inhalers (BAIs): These inhalers deliver medication automatically when the patient inhales through the mouthpiece. They do not require coordination between pressing the canister and inhaling the medication, which can make them easier to use for some patients[32,40,41]. Unfortunately, many molecules and combinations are not available so far.

How to use MDI devices

All MDI devices have a common number of steps in order to succeed with the inhalation. When using an MDI for the first time, it must be primed, pressing the canister to release four times approximately the medication. After that, it does not need to be primed again unless the medication is not used for two weeks or more.

It begins by removing the cap, shaking the inhaler before using, attaching the inhaler to a spacer as needed, holding the inhaler upright, exhaling completely (and very important: away from the inhaler) before inhalation. The device mouthpiece is placed between teeth and sealing lips, making sure to keep the tongue out of the way of the spray. Then a low inspiratory flow must be started, actuating the device a split-second later and then inhaling slowly and deeply. Once reaching the maximum amount of inspiration, breath must be hold (apnea) for five-ten seconds or

for as long as possible, removing the inhaler or spacer from the mouth. Then exhaling and breathing out normally. Steps should be repeated from the complete exhalation for a second puff[42]. Once finished, the cap must be replaced. And it is recommended to rinse the mouth to avoid oropharyngeal deposition of medication.

With BAIs, the inhalation has to be deep and forceful, slightly quicker than MDI[43].

Dry powder inhalers (DPIs)

DPIs deliver medication in a dry powder form that is inhaled by the patient. They do not require a propellant to deliver the medication, they are portable and compact, and are often preferred by patients who have difficulty coordinating their inhalation with the release of medication from an MDI. DPIs can be classified by the number of doses the device can carry or by their intrinsic resistance. The most common classification is by its dosing system.

Types of DPI[44]

There are three types of DPI.

– Single-unit dose DPIs or capsule-based-DPIs: the dose is supplied in individual capsules. Before each administration, the patient has to load the device with one capsule for single-dose delivery. Single-dose DPIs can further be classified as disposable or reusable. Some examples include: Aerolizer®, Breezhaler®, Handihaler®, Zonda® and Glenmark®.

– Multi-unit dose DPIs: they use factory-metered and sealed doses packaged so that the device can hold multiple doses at the same time without having to be reloaded.

  The packaging consists of replaceable disks, cartridges, or strips of foil-polymer blister packaging. Some examples are: Accuhaler® or Diskus®, Ellipta® and Forspiro®.

– Multi-dose reservoir DPIs: they store the powder in bulk and have a built-in mechanism to meter individual doses upon actuation. Some examples are Easyhaler®, Clickhaler®, Novolizer®, Genuair®, Nexthaler®, Spiromax®, Turbuhaler® and Twisthaler®.

DPIs versus MDIs

The decisive factor for therapy success with DPIs, in comparison to MDIs, is the generation of sufficient inspiratory flow to trigger the dosage by de-aggregating the drug formulation from its carrier molecules (generally lactose), creating enough energy to overcome the device-specific resistance and extract the drug from the device and deliver it into the subject[33,45].

DPIs, therefore, have a minimum threshold of optimum flow. They are less appropriate for use during an exacerbation[41].

Unlike MDIs, a patient's inhalation flow profile when using a DPI is typically quick (> 60 L/min) or, depending on the resistance of the device, slightly slower (e.g., > 30 L/min). Quicker inhalation is particularly critical for reservoir/blister-type DPIs, which emit the dose earlier compared with capsule DPIs. Regardless of

speed, the inhalation from a DPI must be deep to achieve optimal drug delivery[31].

However, a number of patients are unable to generate sufficient inspiratory airflow to use their DPIs effectively, resulting in poor drug release and low pulmonary deposition. This is particularly the case for older patients (i.e. > 60 years), children and those patients with severe airflow limitation[45].

The particle size of drug generated by DPIs is another criterion for success that should be considered, as this has implications for drug deposition and clinical efficacy. With DPIs, the respirable particle fraction and consequently drug deposition are dependent on inspiratory flow rate achieved by the patient[46].

Furthermore, the significance of the inhalation speed seems to vary with the particle size. While small particles (i.e., 1.5 mm particle diameter) have a comparable effect on the forced expiratory volume in one second (FEV_1) regardless of the inhalation speed, larger aerosol particles (i.e., 3 and 6-mm diameter) exert a greater bronchodilator effect when inhaled at a slower speed. Slow inhalation speed also resulted in a higher drug penetration index regardless of drug particle size[46].

A major challenge in DPI design is to balance between inhaler resistance and flow rate. In early DPIs, a rapid airflow was required to increase particle deagglomeration by creating more frequent and stronger impactions to achieve a higher fine particle fraction. However, a rapid airflow increases the chances of oropharyngeal deposition and reduces the dose delivered to the lungs. Moreover, high resistances are not suitable for asthma patients who already struggle to breathe[32].

How to use DPI devices

It begins by taking the cap off (some do not have a cap) or by loading the dose of medication according to the system used. The mouthpiece must not be pointed downwards once a dose has been prepared for inhalation. Then proceed with a slow exhalation to empty the lungs, not facing the mouthpiece. A deep, forceful breath must be performed from the beginning, until the maximum amount of inspiratory flow is reached, holding breath for five-ten seconds or for as long as possible and then exhaling and breathing normally. If another dose is required, the steps should be repeated from the slow complete exhalation. Once finished, the cap must be replaced and/or the device closed.

And it is recommended to rinse the mouth to avoid oropharyngeal deposition of medication.

Soft-mist inhalers (SMIs)

SMIs are similar to MDIs in that they deliver a spray of medication, but they use a different mechanism to create the mist. SMIs use a fine mist of medication that is propelled by a spring, rather than a propellant. Examples of SMIs include Respimat.

Nebulizers

Nebulizers are machines that convert liquid medication into a fine mist that can be inhaled by the patient without any effort. They are

often used in hospitals or in patients who have difficulty using MDIs or DPIs. Nebulizers require a power source and take longer to deliver medication than MDIs or DPIs. Examples of nebulizers include Pari LC Plus®, Omron NE-U22V®, and DeVilbiss Pulmo-Aide®.

Selecting an inhalation device for asthma patients[40,45,47]

When selecting an inhalation device for an individual patient, it is necessary to consider whether sufficient inspiratory flow or an effective vital capacity manoeuvre is possible for this patient. If the answer is affirmative, then an inhalation from a DPI would be preferable or, alternatively, a breath-actuated HFA-MDI, possibly in combination with a spacer. If the patient does not have a sufficient inspiratory capacity[45], a nebulizer or an MDI and spacer with a valve are the more suitable choice. Additionally, all guides include and agree that different medications should be delivered from identical devices. If individual combination therapy is unavoidable, combinations of DPIs are preferable to an MDI and a DPI. Ideally, the prescribed inhaler should have a low-to-medium airflow resistance and require minimal patient coordination. Patient preference should also be taken into account when there is a choice among several different inhalation systems.

Patients who have actively participated in and have confidence in their inhaler choice are more likely to use it regularly and correctly.

CONCLUSION

Inhaled medications are the cornerstone of asthma treatment as they provide targeted delivery of medication directly to the lungs, resulting in rapid relief of symptoms with fewer side effects compared to systemic medications. The choice of medication depends on the patient's symptoms and the severity of their asthma.

The main classes of inhaled medications used for asthma treatment are bronchodilators (β-agonists and muscarinic antagonists) and anti-inflammatory agents (corticosteroids). These can be alone or combined, used as rescue or maintenance treatment and on a 12-hour or 24-hour basis. The main molecule for the control of asthma is ICS.

All medications can be delivered through various devices: MDIs, DPIs, SMIs and nebulizers.

While MDI and DPI both deliver medication directly to the lungs, they differ in their mechanism of action and inhalation technique.

DPIs deliver a dry powder form of medication that is activated by the patient's inhalation, while MDIs use a propellant to deliver a mist or spray. DPIs require fast and deep inhalation, while MDIs require slow and steady inhalation. The choice of inhaler depends on the patient's preferences, needs, and ability to use the device correctly.

Proper inhaler technique and regular cleaning of inhaler devices are also essential to ensure optimal medication delivery and control of asthma symptoms.

And, last but not least, patient education and counseling are critical components in optimizing the management of bronchial asthma.

They have been shown to improve patients' knowledge, inhaler technique, adherence to treatment, and clinical outcomes. Healthcare providers should incorporate patient education and counseling into their routine practice to ensure the best possible outcomes for their patients with asthma.

DISCLOSURES

The author declares no conflicts of interest regarding the manuscript.

The author has received honoraria during the last three years for lecturing, scientific advice, and participation in clinical studies for (alphabetical order): AstraZeneca, Bial, Boehringer, Chiesi, Faes, Gebro, Grifols, GSK, Menarini, Novartis, Zambon.

REFERENCES

1. Global initiative for asthma - GINA. 2021.
2. Fernández-Soto JR, Navarrete-Rodríguez EM, Del-Río-Navarro BE et al. Asma: uso adecuado de dispositivos para inhalacion. Bol Med Hosp Infant Mex. 2019;76:5-17.
3. Cazzola M, Page CP, Calzetta L, Matera MG. Pharmacology and therapeutics of bronchodilators. Pharmacol Rev. 2012;64:450-504.
4. Gosens R , Gross N. The mode of action of anticholinergics in asthma. Eur Respir J. 2018;52:1701247.
5. Westby M, Benson M, Gibson P. Anticholinergic agents for chronic asthma in adults. Cochrane Database Syst Rev. 2004;:CD003269.
6. Dekkers BG, Maarsingh H, Meurs H, Gosens R. Airway structural components drive airway smooth muscle remodeling in asthma. Proc Am Thorac Soc. 2009;6:683-92.
7. Buels KS, Fryer AD. Muscarinic receptor antagonists: effects on pulmonary function. Handb Exp Pharmacol. 2012;(208):317-41.
8. Gosens R, Zaagsma J, Meurs H, Halayko AJ. Muscarinic receptor signaling in the pathophysiology of asthma and COPD. Respir Res. 2006;7:73.
9. McIvor ER, McIvor RA. The evolving role of tiotropium in asthma. J Asthma Allergy. 2017;10:231-6.
10. Enerzair Breezhaler autorization by EMA. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/enerzair-breezhaler.
11. Fukunaga K, Kume H, Oguma T et al. Involvement of Ca^{2+} Signaling in the Synergistic Effects between Muscarinic Receptor Antagonists and β_2 -Adrenoceptor Agonists in Airway Smooth Muscle. Int J Mol Sci. 2016;17:1590.
12. Sears MR, Lötvall J. Past, present and future--beta2-adrenoceptor agonists in asthma management. Respir Med. 2005;99:152-70.
13. Tattersfield A.E., Current issues with beta2-adrenoceptor agonists: historical background. Clin Rev Allergy Immunol. 2006;31:107-18.
14. Frielle T, Daniel KW, Caron MG, Lefkowitz RJ. Structural basis of beta-adrenergic receptor subtype specificity studied with chimeric beta 1/beta 2-adrenergic receptors. Proc Natl Acad Sci U S A. 1988;85:9494-8.
15. Johnson M. The beta-adrenoceptor. Am J Respir Crit Care Med. 1998;158(5 Pt 3):S146-53.
16. Robison GA, Butcher RW, Sutherland EW. Adenyl cyclase as an adrenergic receptor. Ann N Y Acad Sci. 1967;139:703-23.
17. Cazzola M. Rogliani P, Matera MG. Ultra-LABAs for the treatment of asthma. Respir Med. 2019;156:47-52.
18. Barnes PJ. Inhaled Corticosteroids. Pharmaceuticals (Basel). 2010;3:514-40.
19. Daley-Yates PT. Inhaled corticosteroids: potency, dose equivalence and therapeutic index. Br J Clin Pharmacol. 2015;80:372-80.
20. Matera MG, Rinaldi B, Calzetta L, Rogliani P, Cazzola M. Pharmacokinetics and pharmacodynamics of inhaled corticosteroids for asthma treatment. Pulm Pharmacol Ther. 2019;58:101828.
21. Wu K, Blomgren AL, Ekholm K, Weber B, Edsbaecker S, Hochhaus G. Budesonide and ciclesonide: effect of tissue binding on pulmonary receptor binding. Drug Metab Dispos. 2009;37:1421-6.
22. Patel R, Naqvi SA, Griffiths C, Bloom CI. Systemic adverse effects from inhaled corticosteroid use in asthma: a systematic review. BMJ Open Respir Res. 2020;7:e000756.
23. Derendorf H, Nave R, Drollmann A, Cerasoli F, Wurst W. Relevance of pharmacokinetics and pharmacodynamics of inhaled corticosteroids to asthma. Eur Respir J. 2006;28:1042-50.
24. Kelly HW, Nelson HS. Potential adverse effects of the inhaled corticosteroids. J Allergy Clin Immunol. 2003;112:469-78;quiz 479.
25. Barnes PJ. Scientific rationale for inhaled combination therapy with long-acting beta2-agonists and corticosteroids. Eur Respir J. 2002;19:182-91.
26. Rogliani P, Cavalli F, Chetta A, Cazzola M, Calzetta L. Potential Drawbacks of ICS/LABA/LAMA Triple Fixed-Dose Combination Therapy in the Treatment of Asthma: A Quantitative Synthesis of Safety Profile. J Asthma Allergy. 2022;15:565-77.
27. Rogliani P, Ritondo BL, Calzetta L. Triple therapy in uncontrolled asthma: a network meta-analysis of phase III studies. Eur Respir J. 2021;58:2004233.
28. Agusti A, Fabbri L, Lahousse L, Singh D, Papi A. Single inhaler triple therapy (SITT) in asthma: Systematic review and practice implications. Allergy. 2022;77:1105-13.
29. Kew KM, Dahri K. Long-acting muscarinic antagonists (LAMA) added to combination long-acting beta2-agonists and inhaled corticosteroids (LABA/ICS) versus LABA/ICS for adults with asthma. Cochrane Database Syst Rev. 2016. 2016:CD011721.
30. Panigone S, Sandri F, Ferri R, Volpato A, Nudo E, Nicolini G. Environmental impact of inhalers for respiratory diseases: decreasing the carbon footprint while preserving patient-tailored treatment. BMJ Open Respir Res. 2020;7:e000571.
31. Peché R, Attar-Zadeh D, Scullion J, Kocks J. Matching the Inhaler to the Patient in COPD. J Clin Med. 2021;10: 5683.
32. Ibrahim M, Verma R, Garcia-Contreras L. Inhalation drug delivery devices: technology update. Med Devices (Auckl). 2015;8:131-9.
33. Haidl P, Heindl S, Siemon K, Bernacka M, Cloes RM. Inhalation device requirements for patients' inhalation maneuvers. Respir Med. 2016;118:65-75.
34. Inhaler Error Steering, Price D, Bosnic-Anticevich et al. Inhaler competence in asthma: common errors, barriers to use and recommended solutions. Respir Med. 2013;107:37-46.
35. Chrystyn H, Price D Not all asthma inhalers are the same: factors to consider when prescribing an inhaler. Prim Care Respir J. 2009;18:243-9.
36. Stein SW, Sheth P, Hodson PD, Myrdal PB. Advances in metered dose inhaler technology: hardware development. AAPS PharmSciTech. 2014;15:326-38.
37. Bousquet J, Dell'anna C. Modulite technology in the development of formoterol HFA pMDI: clinical evidence and future opportunities. Expert Rev Respir Med. 2008;2:27-36.
38. Acerbi D, Brambilla G, Kottakis I. Advances in asthma and COPD management: delivering CFC-free inhaled therapy using Modulite technology. Pulm Pharmacol Ther. 2007;20:290-303.

39. Lewis DA, Ganderton D, Meakin BJ, Brambilla G. Modulite: a simple solution to a difficult problem. Respiration. 2005;72 Suppl 1:3-5.
40. Haughney J, Price D, Barnes NC, Virchow JC, Roche N, Chrystyn H. Choosing inhaler devices for people with asthma: current knowledge and outstanding research needs. Respir Med. 2010;104:1237-45.
41. Laube BL, Janssens HM, De Jongh FH. What the pulmonary specialist should know about the new inhalation therapies. Eur Respir J. 2011;38:1257-70.
42. Cho-Reyes S, Celli BR, Dembek C, Yeh K, Navaie M. Inhalation Technique Errors with Metered-Dose Inhalers Among Patients with Obstructive Lung Diseases: A Systematic Review and Meta-Analysis of U.S. Studies. Chronic Obstr Pulm Dis. 2019;6:267-80.
43. Boise E, Rotella M. ABCs of asthma inhaler and device training. Int Forum Allergy Rhinol. 2015;5 Suppl 1:S71-5.
44. Ye Y, Ma Y, Zhu J. The future of dry powder inhaled therapy: Promising or discouraging for systemic disorders? Int J Pharm. 2022;614:121457.
45. Virchow JC, Crompton GK, Dal Negro R et al. Importance of inhaler devices in the management of airway disease. Respir Med. 2008;102:10-9.
46. Usmani OS, Biddiscombe MF, Barnes PJ. Regional lung deposition and bronchodilator response as a function of beta2-agonist particle size. Am J Respir Crit Care Med. 2005;172:1497-504.
47. Virchow JC. What plays a role in the choice of inhaler device for asthma therapy? Curr Med Res Opin. 2005;21 Suppl 4:S19-25.