Review

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Usability of inhaler devices: a parameter currently misused

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ABSTRACT

Inhalation represents the most convenient route for delivering respiratory drugs. Delivery systems showed a huge technological progress and several pocket inhalers had been engineered over the last decades for clinical use. Despite the growing technological efforts aimed to simplify the inhalation procedures and optimize the therapeutic outcomes, the effectiveness of drug inhalation through inhalers still represents a major challenge in respiratory medicine. Patients may actually incur in different types of critical errors when using all inhalers and are not capable to inhale throughout all devices equally well. Therefore, the choice of the most suitable and convenient device to prescribe still is a critical issue in real life. Usability is the only comprehensive parameter consenting the effective and objective assessment of pocket inhalers' performance, and allowing their objective comparison and ranking. Unpredictable discrepancies are in fact easily detectable between inhalers (even belonging to the same class) in terms of Usability, independently of the patient's awareness. The reasons were described and discussed for each class of inhalers presently available. Usability is a multidimensional parameter that is much more multifaceted and complex than usually presumed. Usability takes origin from the integrated, balanced and objective assessment of the role played by several factors from different domains, such as: factors related to patient's beliefs, to patients' behavioural components, to device engineering and to the overall cost. Usability is the key parameter for assessing and optimizing the appropriateness of any inhalation treatment through whatever device. Usability would also represent a key investigational instrument for supporting the future development of innovative and more performing inhaler devices objectively.

Key words: Usability, Inhaler devices, MDIs, DPIs, SMIs, Respiratory disorders

Introduction

There is consolidated evidence that the inhalation route is the major option for treating acute and chronic respiratory disorders (airway obstruction in particular) as the drugs assumed via inhalation provide some substantial advantages when compared to systemic therapies: they target the lung directly, consent to reduce the delivered dose, promote a quicker onset of action and allows a better therapeutic index [1, 2]. Nevertheless, the delivery of pharmacological agents through inhalers still represents a hot issue in respiratory medicine, particularly for the long-term management of obstructive airway disorders (Bronchial Asthma and Chronic Obstructive Pulmonary Disease - COPD).

In parallel with the development of several innovative molecules, a huge technological progress also occurred in delivery systems over the last decades, mainly aimed to improve the lung deposition of the drug(s) to inhale, to simplify the patients' procedures for a proper inhalation, and to increase the patients' adherence and the compliance to respiratory treatments (Table 1).

Nevertheless, the effectiveness of drug(s) through inhalers still represents a major clinical challenge. The real life

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Table 1. The major evolutive steps of pocket inhalation devices.

1956 the 1st MDI Ricker Lab. 3 M
1960 the ultrasonic nebulizers
1971 the 1° DPI (the Spinhaler)
1980 the 1° spacer device
1987 the Montreal Protocol
1990 the MDIs CFC free
1995 the novel DPIs
2004 the 1° SMI (the Respimat)
2010-2014 the simplified DPIs (oped-inhale-close)
2016 the DuoResp technology
2020 the re-usable SMIs
MID – the Aerosphere technology

effectiveness of inhalation actually depends on several factors, either patient- and device-dependent in origin, that can variably affect and modulate the clinical outcomes, even substantially [3-7]. Unfortunately, despite respiratory drugs are preferably delivered via the inhalation route, the choice of the right inhaler to prescribe still is too frequently guided empirically in real life. In other words, this choice proves usually largely independent of the knowledge of the technological characteristics of the inhalers and of their peculiar performance, still being almost uniquely based on patients' and/or caregivers' perceptions and beliefs [7-9].

The variable engineering of portable inhalers sometimes contributes to magnify the problem as their intrinsic characteristics can peculiarly affect the effectiveness of the therapeutic strategy *per se*. In particular, the capability of inhalers to allow the inhalation of a sufficient respirable fraction of the drug to assume (such as, with a particle size ≤ 6 μ); to ensure a good reproducibility, the precision and the stability of the dose delivered, together with a comfortable usability in daily life still are crucial aspects of the disease management of chronic obstructive disorders, particularly in children and adolescents, in elderly, in fragile patients, and in lower compliant subjects in general [3-6, 7-10]. On the other hand, the improper use of inhalers was showed to influence dramatically the health care impact of respiratory medicine in terms of hospitalizations (+47%); unscheduled visits (+ 62%); courses of antimicrobics and of systemic steroids (+50% and +54%, respectively); working days off (+47%) [11].

A huge number of pocket inhalers, variably shaped, entered progressively the market and are widely used either for delivering single or combined respiratory drugs (Table 1). The technological imprinting of each class of these devices and their peculiar and unavoidable limitations can affect Usability substantially due to several patient- and device-dependent factors [12].

In general terms, three are the basic families of pocket devices presently available: 1) the Metered Dose Inhalers (MDIs): the first inhalers appeared in the '60s for delivering pre-dosed respiratory drugs and still largely used in clinical practice; 2) the Dry Powder Inhalers (DPIs): available since the '70s, they were increasingly prescribed in daily practice for managing asthma and COPD; 3) the Soft Mist Inhalers (SMIs), available since the beginning of the present century and still represented by only one device (the Respimat).

Metered Dose Inhalers (MDIs)

MDIs are the oldest and the cheapest family of pocket inhalers. In the past, a volatile propellant, the chlorofluorocarbon (CFC, such as a class of Freon), was added for allowing the drug emission from the canister. However, as it was stated that CFC contributes to ozone depletion in the upper atmosphere by the Montreal Protocol of 1987 (and confirmed in nine following revisions, up to the Kingali Protocol of 2016), this propellant was replaced by international agreement with the hidrofluoroalcan (HFA) as an environmental safer alternative.

Patients and health care professionals still perceive MDIs as the most intuitive and the easiest devices to use. Unfortunately, the effective inhalation from MDIs highly depends on several factors that are strictly related to the patient's dexterity, cognition and cooperation. The drug emission usually occurs at high speed (around 80km/h) from the canister. Consequently, a sufficient patient's coordination and a sufficient educational level are required for a proper actuation and inhalation. Otherwise, either the lung deposition of

the inhaled drug and the expected clinical results can be significantly compromised. Old patients, fragile individuals, subjects with physical and/or cognitive limitations, children and adolescents (mainly asthmatics, who frequently tend to deny their respiratory handicap and do not accept to spend time enough for improving inhalation procedures), and, in general, those patients not educated to the MDIs' use are not likely to obtain the expected clinical outcomes, independently of the drug(s) prescribed [13].

In real life, both patients and health care professionals (sometimes, doctors included) are too frequently unaware of the major factors that can modify the effectiveness of respiratory treatments to assume or prescribed via MDIs, namely: the high emission velocity of the drug; the coordination needed for achieving the required inhalation flow rate; the variable deposition rate of the drug particulate along the airways, the variability of the dose consistency also due to significant changes in their emitted drug cloud occurring with some MDIs at different filling of the same canister [14]. Moreover, the plume of the drug emitted from the MDI results variable in shape and consistency according to the device peculiarities [15, 16].

All these aspects that are strictly related to the delivery via MDIs are practically unknown to patients who usually base their criteria of judgment on subjective perceptions only. Unfortunately, also the majority of studies carried out for investigating and comparing different MDIs in clinical practice are merely focused on patients' beliefs only, and "perception of inhalation", "ease of use", "preference", "attractivity", or "intuitivity" are the unique variables considered and frequently misused as synonyms of "Usability". The major critical aspects of MDIs' use are reported in Figures 1 and 2.

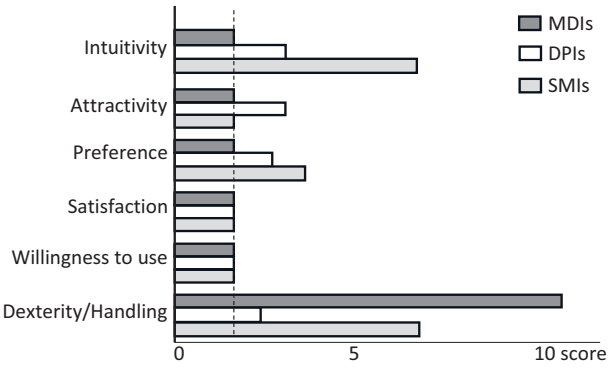

Figure 1. Patient's dependent major critical aspects affecting the judgment of an inhaler device.

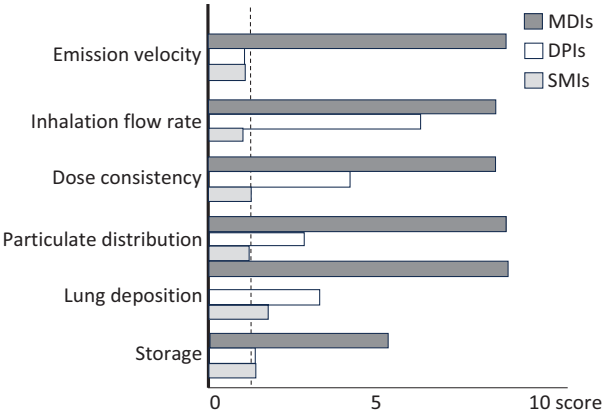

Figure 2. Device dependent major critical aspects contributing to rank inhaler devices.

Dry Powder Inhalers (DPIs)

Since the '70s, but particularly since 1995 when the most innovative DPIs appeared in the market, DPIs represented a valuable step forward in inhalation strategies. On the other hand, they do not require any propellant; inhalation procedures have been simplified in terms of number of actions needed for their actuation, thus being the patient's cooperation and compliance improved. Moreover, a dose counter was added for allowing a higher patients' awareness of residual doses still available in the device; the lung deposition of drugs was increased; the variability of the inhaled dose reduced; the dose consistency optimized, and the incidence of local and systemic side effects quite lowered [17-19].

In the absence of any propellant, either the deaggregation and the aerosolization of dry powdered drugs to inhale depend on patients' inspiratory flow rate (and/or the flow acceleration) generated through the device and on the subsequent pressure drop produced during the forced inspiratory manoeuvre [18-24]: both actions peculiarly related to the technical characteristics of the device.

Consequently, DPIs can be ranked by their technological characteristics, namely: their intrinsic airflow

resistance, their pressure drop/flow rates, and their turbulence generated through the device [6, 25-27]. DPIs can be differentiated by their intrinsic resistive regimen (such as, a constant depending on their original design) as: low resistance (<5 Mbar 1/2 L/min –1; mid); mid resistance (5-10 Mbar 1/2 L/min –1), and in high resistance DPIs (>10 Mbar 1/2 L/min –1) [20, 25].

The de-aggregation of powdered drug(s); the size of particulate to inhale; the lung deposition within the airways, and the dose consistency largely depend on the inspiratory flow rate generated by the patient and the subsequent turbulence produced by the pressure drop occurring inside the DPI [1, 18-22]. As a consequence, the patient is required to produce an inspiratory flow rate (IFR) strong enough for overcoming the peculiar intrinsic resistance (IR) of the device in use.

If the IFR/IR ratio is considered, two are the main conditions leading to an ineffective drug inhalation: 1) a too limited IFR (the upper factor of the ratio) and, 2) a too low IR (the lower factor of the ratio). When IR is too low, the ratio tends to ∞ in these cases and the IFR required for overcoming IR is so high that also healthy individuals can't always reach the threshold needed. Therefore, the message generally assumed that those DPIs characterized by a very low IR should be preferred because more suitable and reliable, are largely misleading in terms of effectiveness of inhalation.

On the other hand, when IR is too high (the lower factor of the ratio), the ratio tends to 0 even if the IFR required is relatively low: in these cases, the strength required to overcome IR can result so high that a large proportion of obstructive patients (i.e., the most compromised in terms of lung function) can't achieve the required IFR in real life due to their limitations in lung mechanics [27].

All these aspects are insufficiently disclosed or neglected even if they highly contribute to DPIs Usability in real life. Moreover, size, volume, gripping, number of manoeuvres required for actuation, and understanding of inhalation procedures make DPIs different from each other: all characteristics that can change substantially the patients' acceptability and usability.

Table 2 reports the most prescribed DPIs listed by their intrinsic resistance and their required inspiratory flow rate, together with the n. of maneuvers needed for their actuation (Table 2), while the major critical aspects of MDIs' use are reported in Figures 1 and 2.

Soft Mist Inhalers (SMIs)

The family of SMIs still is represented by one device only: the Respimat, that is presently also available in its rechargeable version. The drug(s) emitted from

Table 2. Characteristics of different DPIs: n. maneuvers required for actuation; their intrinsic resistance; inspiratory flow rate required for a proper and effective inhalation.

DPIs	n. maneuvers	DPI Resistance ($kPa^{0.5}$ L/min)	Inspiratory Flow Rate (L/min)	
Breezhaler	7	0.017	111	low resistance DPIs
Aerolizer	6	0.019	102	
Accuhaler/Diskus	4	0.027	72	mid resistance DPIs
Novolizer	3	0.027	72	
Ellipta	3	0.028	70	
Genuair	3	0.028-0.031	64	
Spiromax	3	0.031	62	
Turbohaler	4	0.036-0.039	54	
Nexthaler	3	0.036-0.042	54	
Easyhaler	3	0.037-0.042	50	
Clickhaler	3	0.039	50	
Twisthaler	3	0.044	44	high resistance DPIs
Handihaler	8	0.058	37	

the SMI does not need any propellant. In this case the dose delivery is assured by mechanical forces that produce two fine jets of drug solution converging at a pre-set angle. The collision of these two jets generates the typical soft mist emission [28-31].

When compared to MDIs, velocity of emission from the SMI is much lower (5-10km/h) when compared to that one of MDIs, being the risk for patients' insufficient coordination and the incidence of errors of inhalation procedures quite reduced, thus providing a higher Usability. Moreover, the dose consistency proved constant with the SMI regardless of the level of the canister filling [14]. However, also the use of SMIs requires some patient's involvement particularly in terms of dexterity for loading the dose to inhale. The major critical aspects of SMI use are reported in Figures 1 and 2.

The concept of Usability

Although the ideal inhaler still is missing, it was already stated a few years ago that the ideal inhaler should be unavoidably: 1) *effective*: able to consent the inhalation of a sufficient fraction of drug with a particle size ≤ 6 μ, regardless of the patient's inspiratory flow rate produced; 2) *reproducible*: able to always consent the inhalation of the same respirable fraction of the drug; 3) *precise*: allowing the patient to be always aware of the residual doses still available in the device [12]; 4) *stable*: able to protect the drug(s) from the effects of temperature and humidity changes; 5) *comfortable*: easy to transport and use, particularly in critical conditions; 6) *convenient*: containing a number of doses enough to cover a long-term use, and hopefully rechargeable; 7) *versatile*: to be possibly used with different drugs; 8) *environmental compatible*: without any chemical contaminant; 9) *affordable*: of acceptable cost [2, 12].

Anyway, regardless their proximity to the ideal profile, two are the major assumptions on inhaler devices that are definitively consolidated: a) each inhaler presently available is not exempt from some critical errors in their actuation and current use [32], and, b) subjects are not capable to inhale throughout each devices equally well and effectively [33]: in other words the rule "one size fits for all" is not valid with inhalers [23], and can represent a barrier for the proper management or airway diseases. Usually, data on optimal flow rates needed for a proper inhalation are derived from *in vitro* studies that do not always reflect real life conditions. However, even in the presence of normal cognition and manual dexterity, subjects' basic airway and lung conditions may variably affect the extent of inspiratory airflow rate and the performance of inhalers [27]

The concept of Usability just arises from the integrated weighing of all these basic assumptions. In other words, Usability is the comprehensive parameter which is able to reproduce quantitatively the relative role played by all main factors (not merely those patient-dependent, but also those device-dependent) that can affect the performance and the convenience of each device presently available on the market.

As different domains of judgment variably contribute to Usability, its objective assessment does require a multi-domain approach, and can then only take origin from the balanced evaluation of different clusters of factors, variably interacting in the process. Some factors are those mostly depending on the patient's side of the problem (as currently usually done), but other crucial criteria are those involving the knowledge and the awareness of the technical peculiarities of the inhaler (to use or/and to prescribe, respectively), together with those related to the quality of nursing specifically required for allowing the patient to inhale properly and effectively through the device. Moreover, even the patient's socio-economic status and the operational setting should be carefully considered. Finally, the overall cost and its different components also play a role (Figure 3). In particular, differently from what is generally presumed, it does not merely correspond to the cost of the drug. The real life cost should be actually implemented with the cost of resources spent in the educational strategy of the patient (up to making him independent in the proper use of the device) and with the cost of patient's failed outcomes due to the ineffective use of the inhaler prescribed without a sufficient educational approach [34].

All these variables should be extensively checked and weighed because each of them contributes *per se* to

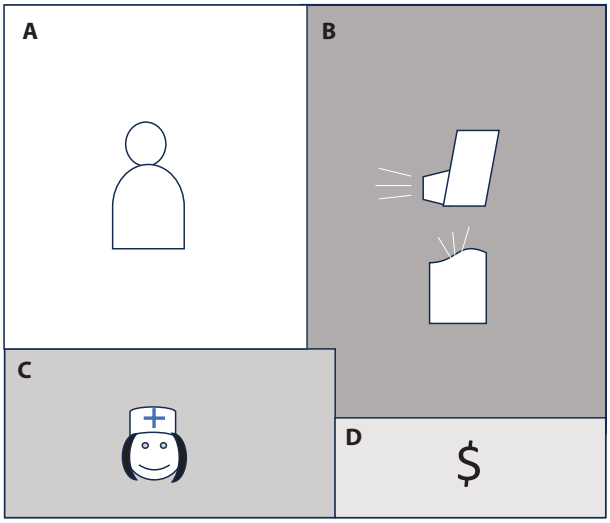

Figure 3. The main components of Usability: a) the patient's dimension; b) the inhalation technology; c) the nursing effectiveness; d) the economic burden.

Usability in real life. Definitively, Usability is a multifaceted parameter consisting of a complex merging of several factors related either to the patient's profile and to the device's characteristics, variably mixed. Only the integrated assessment of all these components will consent health care professionals to ranking and/or comparing objectively inhaler devices in terms of their Usability.

When Usability of inhaler devices are compared by the Global Usability Score (GUS), unsuspected discrepancies are easily found even between devices belonging to the same family, as in the case of MDIs and DPIs, both in asthma and in COPD [35-36]. In these cases, mayor differences in their Usability appears predominantly due to the intrinsic characteristics and engineering of the devices (particularly in the case of DPIs), followed by the quality of nursing provided, and by the overall cost [38-39]. In other words, a substantial dichotomy between the role of patients' subjectivity and the role of objective factors affecting inhalation easily appears and can be quantified in real life in terms of effective Usability.

Unfortunately, the choice (when possible) of the inhaler device to prescribe still is too frequently empirically guided in clinical practice [23], being the technological characteristics and the effective performance of different devices usually underestimated or neglected, while criteria merely based on patients' perception are usually privileged [37, 39-42]. The net result is that, if specific investigational tools are not used, only the patient's viewpoint is currently assumed as corresponding to Usability and is erroneously regarded as a synonymous.

Usability should be much more valued and quantified before prescribing one inhaler as the therapeutic outcomes can be substantially influenced by this choice. Indeed, a recent Delphi Consensus Statement confirmed that the choice of the inhaler should be considered as important as that one of respiratory molecule(s) in terms of disease management of respiratory disorders [11]. In a multinational survey more than 30% of primary and secondary care physicians affirmed to choose the device before considering the respiratory drug to prescribe. Moreover, 87% of UK health professionals claimed their concern about the possible occurrence of problems related to therapeutic prescriptions if the inhaler is not specified, and 86% of physicians were strongly convinced that inhalers are not interchangeable being their unmotivated substitution a frequent cause of negative outcomes [43].

However, it is incredible that the extraordinary evolution in pocket delivery systems observed over the last decades did not match to a proportional improvement of specific instruments devoted to assessing the effects of this technological progress. The GUS questionnaire, particularly in its short and quick version, would represent a reliable response to this unmet need also for clinical purposes. Meanwhile, the patients' subjectivity and beliefs inexplicably remain the only criteria adopted for judging inhaler devices in the large proportion of cases and of clinical studies. Therefore, the true assessment of Usability still represents a hot issue indeed, while it should recognize a primary position in the decisional pathway for deciding the appropriateness of therapeutic strategies (Figure 4).

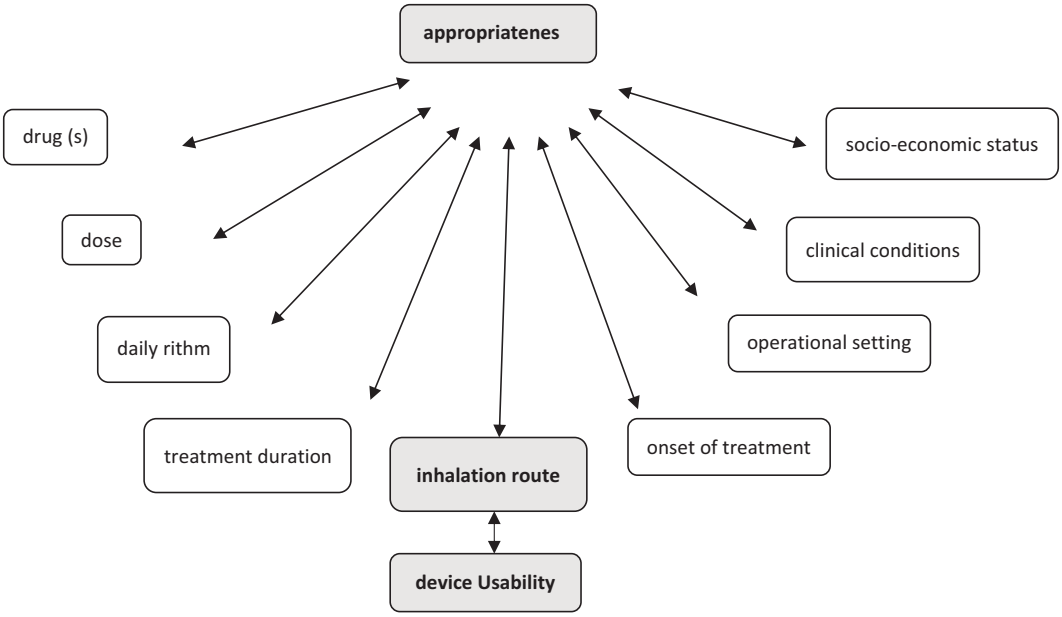

Figure 4. Positioning of device Usability within the decisional pathway for the appropriateness of respiratory therapeutic interventions.

Conclusions

The choice of the most suitable inhalation device to prescribe still is a complex issue indeed. Usability is the multidimensional parameter that could integrate and quantify the role of all decisional components, such as, device technology, patient's beliefs and behaviours, and overall cost.

As Usability is largely independent from subjective factors, it would represent a helpful tool for comparing and ranking the performance of inhalation devices on an objective basis. Usability can then be regarded as an extraordinary tool for supporting doctors and other health care professionals in their operational decisions in clinical practice, fully according to the concept of personalized therapy.

Finally, Usability would be used as a key investigational tool for supporting and stimulating the incoming development of novel and more performing inhalers in the next future objectively.

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