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Review Article

Why is Patient Usability the Key to Inhalation Device Development?

Roberto W Dal Negro*

National Centre for Respiratory Pharmacoeconomics and Pharmacoepidemiology, Verona, Italy

***Corresponding Author:** Roberto W Dal Negro, National Centre for Respiratory Pharmacoeconomics and Pharmacoepidemiology, Verona, Italy.

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Abstract

Inhalation is the most convenient route for administering respiratory drugs. As a consequence, delivery systems had been progressively improved and several pocket inhalers progressively engineered (Metered Dose Inhalers - MDIs; Dry Powder Inhalers - DPIs, and Soft Mist Inhalers - SMIs). Anyway, the effectiveness of drug inhalation still remains a challenge in clinical respiratory medicine. Different types of patients' critical errors are common with all inhalers presently available and patients do not inhale throughout all devices equally well. The choice of the most suitable device to prescribe still is a challenging issue in clinical terms as the role of several factors affecting the effectiveness of inhaler devices should be evaluated, further to the patient's beliefs only.

Usability is the parameter capable of providing the assessment, comparison and ranking of pocket inhalation devices comprehensively and substantial differences among inhalers are easily detectable independently of patient's awareness. The Global Usability Score represents a much more multifaceted parameter than presumed as it consists of the integrated assessment of several factors that are related to the device engineering, to patient's perceptions, to some behavioural patients' and care-givers' components, and also to the economic convenience. Usability provides the key parameter for investigating the true effectiveness of any inhalation device and a key tool for optimizing the future development of novel and more performing inhalers.

***Keywords**: Usability; Inhalation Devices; MDIs; DPIs; SMIs; Respiratory Disorders*

Introduction

The effectiveness of respiratory drugs administered through inhalation devices still represents a crucial topic in respiratory medicine, particularly for managing obstructive airway disorders (Bronchial Asthma, Chronic Obstructive Pulmonary Disease - COPD, and emphysema). It is in fact accepted since long ago that the inhalation route provides a better therapeutic index because, when inhaled, respiratory drugs target directly the lung; allow a lower active dose and consent a rapid onset of action [1,2].

We witnessed a tremendous progress in technology of inhalation devices in the last years, mainly aimed to improving the lung deposition of the drug(s), simplifying the patients' procedures for inhalation, and favouring the adherence to therapeutic strategy.

Several pocket devices are presently available for delivering single or combined respiratory molecules. However, it should be emphasized that the ideal device should satisfy nine major criteria. It should be: a) effective, such as capable of consenting the inhalation of a sufficient drug fraction characterized by a particle size ≤ 6μ, regardless of the patient's inspiratory flow rate; b) reproducible: such as consenting to inhale systematically the same amount of drug and the same respirable fraction; c) precise: such as allowing the patient

to always know the doses to inhale still available in the device; d) stable: capable to protect the drug(s) from high temperature and humidity; e) comfortable: easy to use in various setting of daily life (particularly in critical conditions); f) convenient: such as filled with drug(s) doses enough for covering a long-term use, and even rechargeable; g) versatile: possibly usable for different respiratory drugs; h) environmental compatible: such as devoid of any contaminant; i) affordable: such acceptable in terms of cost [2].

The structural peculiarities of inhalers represent a crucial issue from this point of view as the delivery of a proper respirable fraction of the drug to inhale may be differently affected and variably affected can also result the disease management of respiratory disorders to treat [3-7]. Nevertheless, several factors (both patient- and device-dependent) still impact on the effectiveness of drug(s) inhalation in real-life and consequently on the clinical outcomes expected [3-6]. In effect, the improper use of inhaler devices may lead to a substantial impairment of indices of health care burden: +47% hospital admissions; + 62% emergency visits; +50% and + 54% antibiotic and systemic steroids prescriptions, +47% absenteeism [8].

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Anyway, two are the main assumptions to keep in mind in real-life respiratory medicine: 1) different types of critical errors are possible with all inhalers [10] and, 2) patients are not capable to inhale throughout all devices equally well [2,10,11].

Pocket devices can be grouped in three major families for delivering single or combined respiratory active drugs: a) the Metered Dose Inhalers (MDIs): available and widely used since the '60s for delivering pre-dosed respiratory molecules; b) the more recent Dry Powder Inhalers (DPIs); c) the Soft Mist Inhalers (SMIs), the most recent class of pocket inhalers, only represented by one device (the Respimat).

Just before facing the issue of usability, a short overview of the main characteristics and limits of each class of these pocket devices was reported.

MDIs

MDIs are the oldest and the cheapest family of pocket inhalers. The drug emission from the canister needs a propellant (CFC in the past, presently HFA).

Patients and also the majority health care professionals usually perceive these devices as the easiest way for delivering respiratory drugs. Unfortunately, the proper and effective use of MDIs is difficult indeed. Their effectiveness highly depends in fact on several aspects variably related to patient's subjectivity, physical conditions, and cooperation (such as: the patient's preference, intuitivity, perceived ease of use, cognition and dexterity above all).

The drug(s) cloud is usually emitted from the canister at high speed (around 80 km/h). A good patient's coordination is obviously needed for obtaining an effective inhalation from the MID and this aspect represents a true critical point for the majority of cases because it requires a lot of time for the patients' training. Otherwise, both the lung deposition of the inhaled drug within the airways. As a consequence, the expected clinical effect can result frequently compromised in particular real-life conditions, such as: in old and fragile

individuals; in patients with physical and/or cognitive limitations; in teen agers (i.e. in asthmatic adolescents who frequently "refuse" their respiratory disorder and do not accept to spend some of their time for learning the correct inhalation procedures and for training) [12]. Unfortunately, patients and many health care professionals (doctors included) are frequently unaware of the major limitations of MDIs' use, respectively used or prescribed. In particular, the consistency of the dose can be dramatically variable with some MDIs, due to significant changes in their emitted drug cloud occurring at different fillings of the same canister [13].

Most of these critical aspects of the drug delivery from MDIs are usually unknown by the majority of patients who largely base their criteria of judgement on MDIs use on their subjective perceptions (such as: the perception of inhaled fresh air, good or bad taste, etc.). Unfortunately, a great proportion of clinical studies planned for comparing the performances of different MDIs merely focused the role of patients' beliefs only, while disregarded the role of all other factors of variability. In all these cases the term "usability" was misused, ore erroneously introduced as a synonymous of "attractivity", "ease of use", or "preference".

DPIs

DPIs represented a true improvement in inhalation strategies as they fit with the majority of general "best criteria" mentioned above. Though largely variable in shape, they avoided any propellant; introduced a quite visible dose counter; simplified and minimized the inhalation procedures needed for a proper inhalation; largely reduced the role of patients' cooperation and consequently improved the patient's adherence to treatment. But the true basic advantages achievable with DPIs and substantially affecting the therapeutic strategy were: the enhanced deposition of inhaled drug(s) within the lung; the reduced variability of the inhaled dose; a more stable consistency of the dose emitted, and the reduction of local and systemic side effects [14-17]: all results of relevant clinical value.

As DPIs do not need any propellant for the drug emission, the de-aggregation and the aerosolization of the dry powder to inhale mostly depend on the patient's inspiratory flow rate generated through the device and on the subsequent pressure drop produced during the forced inspiratory manoeuvre [18-23].

DPIs can be distinguished by their intrinsic airflow resistance, pressure drop/flow rates, and turbulence generated inside the device, all peculiarities depending of their intrinsic structural characteristics [24-26]. DPIs are usually identified by their intrinsic resistive regimen (that is a constant depending of the original engineering) in three groups: the low resistance (< 5 Mbar 1/2 L/min^{-1}; mid); the mid resistance (5 - 10 Mbar 1/2 L/min^{-1}), and the high resistance DPIs (>10 Mbar 1/2 L/min^{-1}) [18,25]. To keep in mind that the disaggregation of the powder to inhale; the particles size of the powder; the consistency of the dose, and the amount of drug(s) within the airways largely depend on the inspiratory flow rate generated by the patient and on the turbulence created by the pressure drop inside the device [1,18]. Consequently, the peculiar intrinsic resistance (IR) of the DPI could be overcome only if the patient's inhalation performed through the DPI will be strong enough to produce a proper inspiratory flow rate (IFR). The IFR/IR ratio regulates the 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 ∞ and the IFR required in these cases for overcoming the IR is so high that also healthy individuals can't frequently achieve the needed threshold limit. In other words, the message too easily assumed that those DPIs characterized by a low or very low IR should be preferred because more usable, is largely misleading in terms of real-life Usability. On the contrary, when IR is too high (the lower factor of the ratio), the ratio tends to 0 though the required IFR is relatively low. The strength required to overcome IR can result so high in these cases that a not negligible proportion of patients (such as, those with the most compromised lung function) are not capable to perform the required IFR because of their limitations in lung mechanics [27]. Table 1 reports the rate of intrinsic resistance and the required inspiratory flow rate claimed for each of the most used MDIs, together with the n. of manoeuvres needed for their proper actuation.

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	
Novolizer	3	0.027	72	
Ellipta	3	0.028	70	
Genuair	3	0.028-0.031	64	Mild resistance DPIs
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	

Table 1: *Characteristics of different DPIs: their intrinsic resistance; inspiratory flow rate required for a proper and effective inhalation; n. manoeuvres required for actuation (from Ref. 17 and 24).*

SMIs

The family of SMIs presently consists of one device only: the Respimat, that also has the advantage to be rechargeable. 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].

The drug(s) emission occurs at a much lower speed (5 - 10 km/h) with Respimat, thus requiring a lower level of patients' coordination for a proper actuation and causing a lower incidence of errors. The dose consistency is constant with Respimat independently of the filling rate of the canister [13]. Nevertheless, also Respimat requires some degree of patient's involvement, particularly when loading the dose to inhale.

Usability

The concept of usability stems from the comprehensive analysis of all basic information reported above as the performance of each inhaler device depends on several parameters belonging to different domains of judgment that contribute to the global assessment of Usability. As a consequence, the true assessment of Usability requires a multi-domain approach and the objective evaluation of several factors, variably interacting: 1) those mainly affected by the patient's side of the problem (as usually done); 2) those related to the knowledge and the awareness of the technical characteristics and limitations of the devices; 3) the quality of nursing specifically provided to the patients; 4) the patient's cultural and socio-economic conditions; 5) the operational setting: 6) the economic convenience of the device and drug to prescribe and to use that not merely correspond to the cost of the drug as frequently presumed (Figure 1).

In other words, Usability emerges as a complex and multifaceted parameter affected by several patient's, technological and pharmacoeconomic factors variably mixed, that should be carefully integrated and assessed before whatever comparison between different devices in terms of their effectiveness. For the reasons the Global Usability Score (GUS) was defined and validated a few years

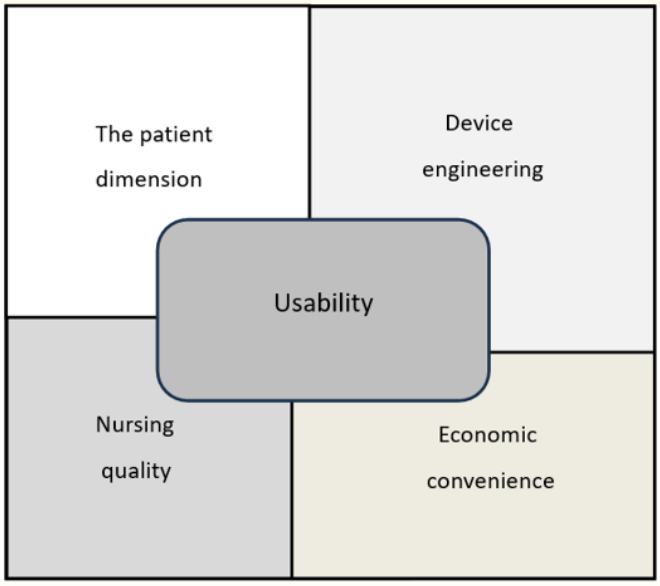

Figure 1: *Usability as a multicomponent parameter.*

ago in the aim to provide a rapid and comprehensive parameter capable to support the choice of the most convenient device to prescribe stemming from the weighted and objective evaluation of all major factors (but not only of those dependent on patient's subjectivity) affecting Usability [32].

Surprisingly, when devices belonging to different families (or even to the same family, i.e.: the DPIs) are compared by their true Usability, unsuspected discrepancies are found [13,33-35]. These differences in Usability are mainly due to the intrinsic peculiarities of devices, to the quality of nursing previously provided to the patient, and to related economic [34,35].

Unfortunately, the choice of the inhaler device to prescribe still is frequently empiric in clinical practice: the technological characteristics and the effective performance of different devices are usually underestimated or neglected, while only criteria merely based on patients' perception are privileged [36-45].

The assessment of usability of inhaled devices still represents a crucial issue indeed despite the great improvement of delivery systems, generally aimed to improving the patients' adherence to treatments and the therapeutic outcomes. To emphasize that in also a recent Delphi Consensus Statement, the specific role of inhalers should be presently regarded as important as that one of respiratory molecules in terms of disease management of respiratory disorders [8].

Conclusion

Usability is a multidimensional parameter consisting of the balanced and integrated assessment of several aspects peculiarly related to devices' technology, patient's beliefs, behavioural components, and cost. All these factors have a substantial role in defining the appropriateness and the effectiveness of the best device to prescribe and to use in clinical practice.

Usability rises as a key step to be included in the global decisional path aimed to check and optimize the appropriateness of whatever respiratory therapeutic strategy via the inhalation route. Usability also represents an extraordinary tool for supporting doctors and other health professionals in improving their interpersonal relationships with respiratory patients as it represents a valuable opportunity to

motivate self-management and provide patients with objective information and warnings concerning their respiratory therapy. Finally, Usability can work as a key investigational instrument for supporting and stimulating the incoming development of novel and more performing inhalers in the next future.

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