Review Article

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Digital Pressurized Metered-dose Inhalers Define Adherence, Prevents Pseudo adherence In Obstructive Airway Disease Management!

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Abstract

Aerosol therapy and OAD: Inhalers play a crucial role in the management of patients with obstructive airway disease (OAD), and it is being recognized that the choice of the inhalation device appears to be as important as that of the drug molecule.

Aerosol therapy in OAD management has undergone renaissance with the wide availability of several drug delivery platforms including dry powder inhaler, pressurized metered-dose inhaler (pMDI), soft mist inhalers, and portable vibrating mesh nebulizers. The aerosol dynamics allows targeted drug delivery while avoiding the systemic side effects, first-pass metabolism at 1/10th the dosage under controlled settings without compromising on the quick therapeutic action in most of these cases.

Since OAD remains progressive disease with persistent or diurnal symptoms due to divergent and varied pathobiologic or overplaying risk factors, choice of inhaler therapy in most of these cases remains a clinical challenge. Notwithstanding the clinical challenges of actuator and breath (inhalation) coordination in pMDIs, they have remained the primary choice of therapy in most cases of progressive or recurrent exacerbations who have relatively low inspiratory flow rates (<30 L/min).[1]

However, nonadherence rates for long-term inhaler therapy among adults are estimated to exceed 50%. Nonadherence is associated with unfavorable clinical outcomes and diminished quality of life. Lack of a dose counter makes determining the number of remaining doses in an MDI problematic. The addition of an simple, accurate, and reliable digital dose counter to an inhaler can improve patient satisfaction.

Key words: Bronchial Asthma, Digital dose counter pressurized metered-dose inhaler's, Nonadherence, Obstructive airway disease, Pseudo adherence

INTRODUCTION

OAD: Asthma Control Status

Asthma is one of the most common disease encountered in clinical practice. An estimated 300 million people suffer from asthma worldwide, and an additional 100 million new cases will be added by the year 2025 with the bad news further that the Current Asthma status seems to be poorly controlled.[2-4]

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In AP-AIM study by Gold *et al.* [Table 1], it was found that India and China (0% and 2%, respectively) had the lowest proportion of patients with "Well-controlled" asthma. Furthermore, patients with partly and uncontrolled asthma missed significantly more days of work or school in the previous year (an average of 3.7 and 7.9 days) compared to patients with well-controlled asthma (average of <1 day).[5]

The recent REALISE Asia Survey on partly or uncontrolled asthma control status based on GINA suggested questionnaire on asthma control again highlighted the disparity in well control status as just 50%.[6]

Indian asthma patients have a high frequency of reported exacerbations (67%), leading to substantial functional, emotional limitations, and uncontrolled status.[7,8] This depicts poor control of asthma and reflects the inadequate treatment of such patients.

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Table 1: Epidemiological surveys assessing asthma control status worldwide

Studies	Region	Uncontrolled (%)	Partly controlled (%)
AIRIAP-2	Asia and India	35	62
AP-AIM	Asia and India	40	60
REALISE-Asia	Asia	50	32
EUCAN-AIM	EU	24	58

AIRIAP-2: Asthma insights and reality in Asia-Pacific, AP-AIM: Asia-Pacific asthma insights and management, EUCAN-AIM: Europe and Canada asthma insights and management

In ARIAP – 2 study, it was significant that inadequate assessment of control is an important factor leading to poorly controlled asthma. Not only do many patients overestimate their level of asthma control but clinicians also tend to do the same. These findings indicate a need for simple, reliable tools to measure asthma control. Furthermore, it was found that out of 4805 individuals screened for asthma, 4663 (97%) individuals had poorly controlled asthma.[9]

ASTHMA CONTROL AND PSEUDO ADHERENCE

Although nonadherence related to device coordination (inhalation-actuation), drug habituation and side effects to the inhaled medication seem to be common risk factors for poor compliance, pseudo or incomplete adherence continues to be playing an equal part in this equation for uncontrolled symptoms and related clinical outcomes.

Pseudo adherence refers to the clinical situation when patients start using the pressurized metered-dose inhaler (pMDI) beyond the stated label dosages for the inhaler canister with consequent exposure and inhalation of "empty" propellant (HFA) sprays that contain declining concentration of active drug, i.e., "Tail"ed sprays.

In a study by Ogren *et al.*, it was found that up to 40% of patients believe they are taking their asthma medication when they actually are activating an empty or nearly empty MDI.[10]

Rubin and Durotoye asked clinic patients how they determined that the MDI was empty, and 72% reported the MDI was empty if there was no sound when the canister was actuated.[11]

Tail off refers to the clinical phenomenon when drug delivery from MDI becomes inconsistent, variable or unpredictable when the recommended doses become exhausted, and the patient is exposed to the aerosol spray containing propellant or excipient's only [Figure 1]. This often leads to suboptimal

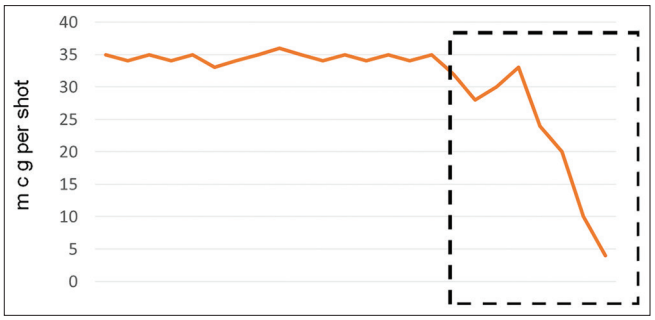

Figure 1: "Tail off" characteristics with inconsistent delivery of medications

response with continued threat of exacerbations or symptoms of dyspnea in patients with chronic obstructive pulmonary disease or bronchial asthma due to overriding, creeping uncontrolled inflammation in the airways.

Current strategies to avoid tail off seem to be rudimentary or predated with patients often "Guesstimating" the content or volume of spray by shake and listening or visualizing the actuation spray. Nearly ≈70% patients continue to follow these "age-old practices" that are not approved, advocated or validated by any regulatory body including food and drug administration (FDA).[12]

In a study by J.B. Connor and Buck, it was found that 87 patients (82%) considered their MDI empty only when nothing came out of it, making it likely that they were inhaling only propellant for many doses, thereby increasing their risk of prolonged bronchoconstriction and airflow limitation requiring urgent care.[13]

PSEUDO ADHERENCE: INTERNATIONAL AND NATIONAL PERSPECTIVE

International Perspective

US FDA in its Guidance statement to the Industry has advocated the incorporation or integration of dose counters in pMDI since accurate and consistent tracking of the doses seems to be only way to determine the remaining doses in the MDI. These dose counters should be engineered to reliably track the doses that have delivered by "complete" actuations to ensure that there is 100 percent accuracy in the dose delivered to the patient in the "right" quantity.[14] Similarly, EMEA has recommended a mechanism to convey information on the "start point" of tail off spray that should be provided with these devices.[15]

National Perspective

The CAPA survey results recently presented @ NAPCON '16 by Singh and Krishnaprasad on behalf of 202

nationally representative sample of pulmonologists in India again highlighted the pertinent issues of non- and pseudo-adherence in real-world clinic settings of India where most doctors (71%, n = 100) agreed that patients utilize the current conventional pMDIs including the dose counter analog devices till the "last" spray thereby exposing them to risk of "persistent" symptoms and/or exacerbations.[7]

Digital pMDIs: Defines Adherence Prevents Pseudo Adherence

The situation is further compounded by the lack of feasible or practical options in real-world settings for the patient to assess and avoid pseudo adherence.[16]

The digital dose countered pMDIs [Figure 2] offer a large digital display for easy accessibility and comprehension by the varied patient population utilizing the device including elderly. Second, the "end" display at the exhaustion of the labeled 120 dosages heralds the start of the subtherapeutic tailed sprays that the patients' needs to avoid. This seems to be of therapeutic relevance in our real-world settings while assessing the current referral cases of partly or uncontrolled cases for any other differential diagnoses.

Digital pMDIsClinical Evidence

The clinical impact of digital pMDI was assessed and reviewed by the DUSS panel involving ≈500 doctors across India, and they found that these devices offer significant improvement in the asthma status that was either newly diagnosed or poorly controlled with conventional therapy or devices.

DUSS ANALYSES

Aim

The aim of the study was to assess the clinical impact and utility of digital pMDIs in newly diagnosed or poorly controlled patients of bronchial asthma.

Study Design

A cross-sectional, national, prescription, retrospective, and cohort analyses as drug utilization surveillance study for Digital pMDIs with DUS survey sheet was carried out @ 500 outpatient centers across India during Sept '16. *Post hoc* analyses for categorical data were carried out by Fisher's Exact Test utilizing QuickCalcsGraphpad Prism version 7 software.

Results

A total of 5195 consecutive patient records on digital pMDIs were available for full set analyses. Baseline demographics included males (69.1%)/females (30.9%), mean age and body weight of 46.7 years and 60.9 kg with many on FB (3791; 73%) compared to SF (1404; 27%) combination. Baseline status and further clinical response

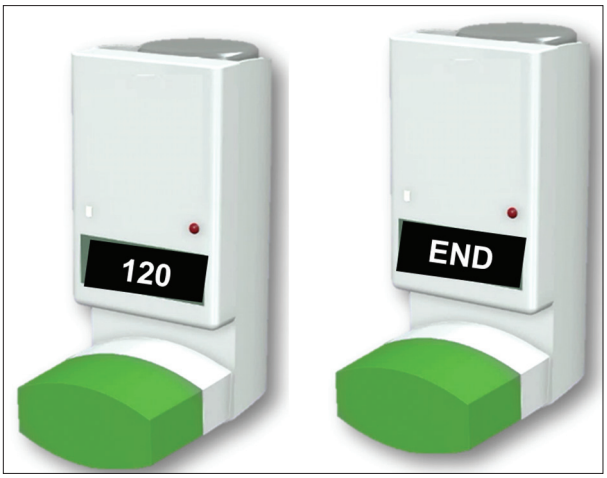

Figure 2: Digital dose counter pressurized metered-dose inhalers with "END" display signifies "START" of "Tail"ed sprays!!

assessment utilizing GINA assessment questionnaire were available for 4575 patients. Patient records with baseline and further clinical response assessment records with GINA Assessment questionnaire for daytime, nighttime, activity limitation and need for rescue medication were taken for analyses. Baseline mod-to severe bronchial asthma status categorized as newly diagnosed or poorly controlled asthma was documented in 2445 (47.1%) and 2750 (52.9%) cases, respectively.

- Baseline Poorly controlled subgroup analyses: Baseline demographic details highlighted the clinical preference for FB compared to SFC formulations in the poorly controlled subgroup [Figure 3].·
  Following therapy with digital pMDI based regimen, "well control" status was observed in 92.7% and 90.3% cases for overall (n = 2942) and baseline poorly controlled patients (n = 1708), respectively, at the end of 8 weeks. For 219 patients with baseline uncontrolled asthma status, initiation with digital pMDI "exclusively" improved well control status in 76.3% cases who were initially on conventional pMDIs devices.

Again the well control asthma status was dramatically and more significantly improved with Xanthines (n = 840) compared to LAMA (n = 369) supplementation in 95.2% and 85.9% cases, respectively (P = 0.0001) [Figure 4]. Adverse events (106, 2%) of mild-to-moderate intensity involving Tremors (34;0.7%), Palpitation (10;0.2%), Mouth ulceration (10;0.2%), and Oral candidiasis (9; 0.2%) were reported. Nebulization was required in two cases with episodic breathlessness and discharged with no consequent sequelae. The authors concluded that Digital pMDIs treats "pseudo severe asthma".[17]

- Baseline newly diagnosed subgroup analyses: A total of 2445 patient records categorized as newly diagnosed Br. asthma were analyzed. Baseline demographics included males (1555;63.5%)/females (791; 32.3%), mean age of 43.7 years prescribed with FB (1863; 76.2%) or SF (582; 23.8%) along with or without xanthines and /or LTRAs/antihistaminics formulations.
  Following therapy with digital pMDI based regimen, uncontrolled status was observed in 5%, 1.5 %, and 1.1% cases for patients on digital pMDI alone, complimentary xanthines, or LTRAs/antihistaminic formulations, respectively [Figure 5].

Adverse events (28, 1.1%) of involving tremors (7; 0.3%), palpitation (1; 0.04%), dysgeusia, (5, 0.2%), dysphonia (4, 0.2%), nausea (3,0.1%), and mouth ulceration (2;0.1%) were reported. Nebulization was required in one case that resolved with no sequelae [Figure 6]. The authors concluded that digital pMDIs offers a simplified solution in tracking nonadherence in real-world settings and avoids or prevents patients from falling prey to pseudo adherence for continued well-controlled status when they are compliant to the doctor instructions.[18]

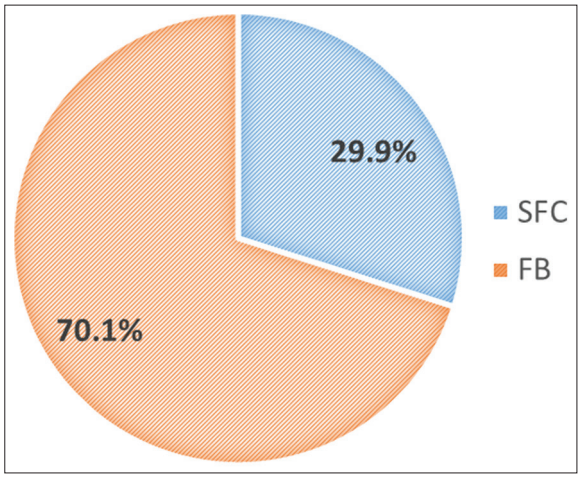

Figure 3: Inhaled corticosteroid/long-acting -agonist digital pressurized metered-dose inhaler utilization for poorly controlled cases

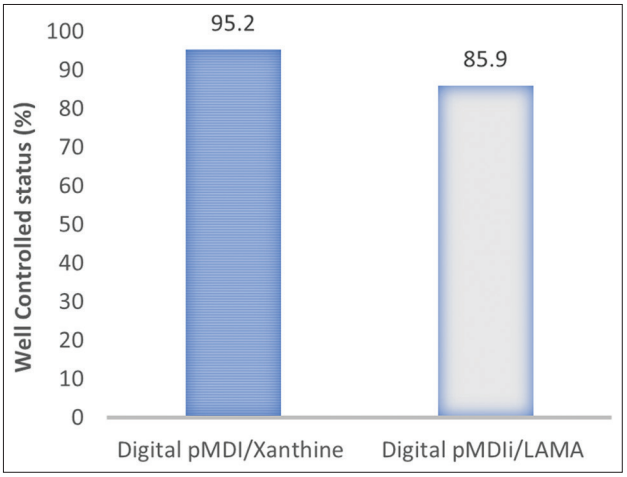

Figure 4: Well-controlled status for poorly controlled grp @8 weeks

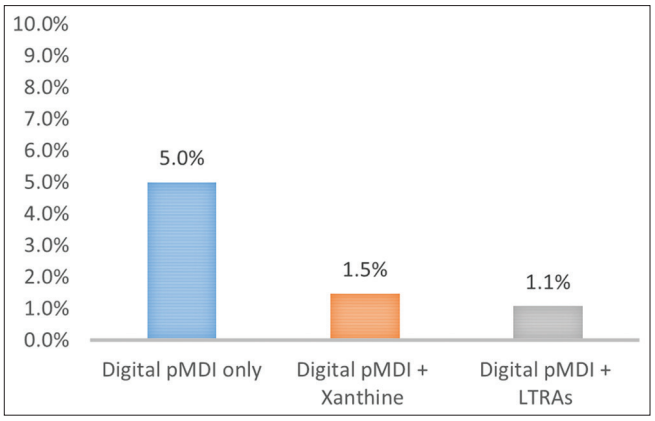

Figure 5: Uncontrolled Br. asthma rates@8 weeks

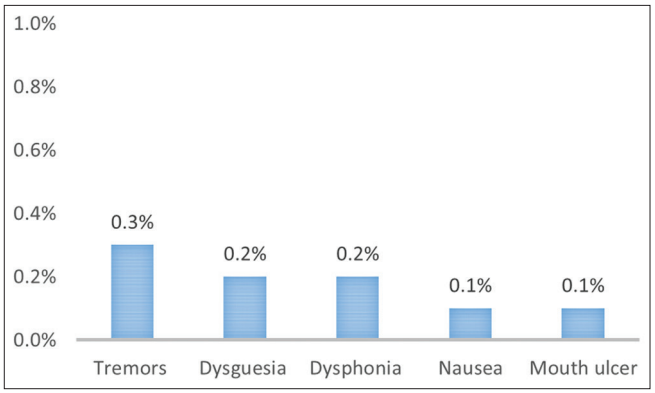

Figure 6: TEAEs observed @8 weeks

CONCLUSION

Current strategies to assess patient adherence or nonadherence remain rudimentary with no precision on the tracking mechanisms for "Tail off" phenomenon. US FDA and EMEA recommend use of pMDIs that offer reliable information on "Tail off" and "dosage delivered." The addition of a simple, accurate, and reliable digital dose counter to an inhaler can improve patient satisfaction by offering reassurance and added confidence that their medication can be relied on, as well as reducing the risk of patients taking a subtherapeutic dose using the inhaler past the label claimed number of doses.

Tracking pseudo adherence reliably and accurately with digital pMDIs "assures" therapeutic response to inhaled corticosteroid/long-acting β-agonist.

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