

## REVIEW ARTICLE

# 'Powering Precision' in OAD Management... *from Diagnosis to Delivery*

Talwar D<sup>1</sup>, Katke P<sup>2</sup>, Krishnaprasad K<sup>2</sup>

## Abstract

Achieving asthma control remains an elusive goal for the majority of patients worldwide. Pressurized metered-dose inhalers (pMDIs) are the cornerstone of asthma treatment. Despite a better understanding of the pathophysiology of asthma, presence of reliable diagnostic tools, availability of a wide array of effective and affordable inhaled drugs and simplified national and international asthma management guidelines, asthma remains poorly managed in India. 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. The pMDI is an economic and portable medication delivery system, but the device does not indicate how much medicine remains in the canister once a patient starts using it. 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. More trials are needed to determine the merits of different treatments and strategies for patients with inadequately controlled severe persistent asthma and to identify patients likely to benefit from new treatment options.

## Obstructive Airway Disease (OAD): Growing Disease Burden

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.<sup>1</sup>

Inhalers play a crucial role in the management of patients with OAD and it is being recognized that the choice of the inhalation device appears to be as important as that of the drug molecule.<sup>2</sup>

The current burden of OAD (2016)

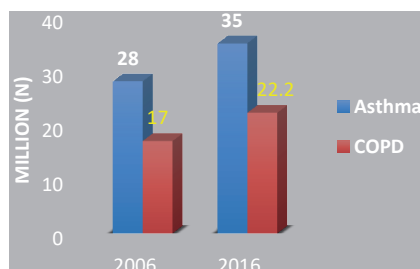


Fig. 1: Disease burden of OAD in Indian children

involving 3.5 and 2.2 crore Indians with Bronchial asthma or COPD (Figure 1) represents the galloping strides that these airway diseases are making especially in context to Hypertension or Cardiometabolic disorders that the Indian subcontinent is facing. The prevalence of asthma has been estimated to range 3-38% in children and 2-12% in adults,<sup>3</sup> being the commonest chronic disorder among Figure 1. A recent Indian Study on Epidemiology of Asthma, Respiratory Symptoms and Chronic Bronchitis (INSEARCH) done with 85,105 men and 84,470 women from 12 urban and 11 rural sites in India estimated the

prevalence of asthma in India to be 2.05% among those aged >15 years, with an estimated national burden of 18 million asthmatics.<sup>4</sup>

## OAD: Asthma Control Status

Achievement and maintenance of control through the assessment of clinical manifestations and future risk has become the aim of treatment over the years.

In AP-AIM study by L.S. 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. Also 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).<sup>5</sup>

The recent REALISE ASIA Survey on Partly or Uncontrolled asthma Control status based on GINA suggested Asthma Control Questionnaire assessed telephonically again highlighted the disparity in Well control status as just 50%.<sup>6</sup>

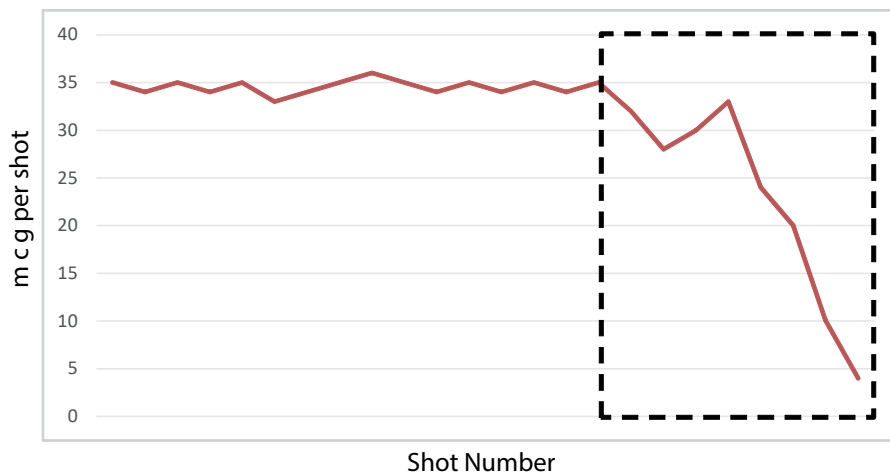
In Indian epidemiological survey done across 202 pulmonologists, it was clearly found that nearly half of the currently managed cases were perceived to be Partly controlled asthma by 143 (71%) pulmonologists. Patient noncompliance seemed to be the important pertinent reason in most of these cases.<sup>7</sup>

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%

<sup>1</sup>Senior Consultant Pulmonologist, Director and Chair, Metro Respiratory Centre, Noida; <sup>2</sup>Medical Services, Glenmark Pharmaceuticals Ltd., Mumbai, Maharashtra

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**Fig. 2: 'Tail off' characteristics with inconsistent delivery of medications**

Indian asthma patients have a high frequency of reported exacerbations (67%), leading to substantial functional and emotional limitations.<sup>8</sup> This depicts poor control of asthma and reflects the inadequate treatment of such patients.

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, clinicians also tend to do the same. These findings indicate a need for simple, reliable tools to measure asthma control. Also it was found that out of 4805 individuals screened for asthma, 4663 (97%) individuals had poorly controlled asthma.<sup>9</sup>

### Asthma Control: Current Challenges

- Disease progression:** ACOS, Neutrophilic Asthma or concomitant Allergic rhinitis often requires differential management strategies. Similarly the role of Biomarkers including Blood eosinophilia is well highlighted in patients with COPD exacerbations. Similarly the CRP levels seems to well reflective of the need for antibiotics in patients with COPD exacerbations
- Device strategy:** Patients with unstable disease course or uncontrolled symptoms are better responsive to MDI strategy compared to DPI since the inspiratory flow rate is compromised in most of these patients

- Patient Compliance:** 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.

### Asthma Control and Pseudoadherence

Pseudoadherence refers to "Patients who think that they are taking their medication when they actually are activating a nearly empty canister". This problem can result in patients continuing to use the inhaler when it may no longer be delivering the required dose. In a study by Ogren RA 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.<sup>10</sup>

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.<sup>11</sup>

Despite the perception and availability of 'Dose counter' pMDIs in the market, most pulmonologists (n=100, 71%) perceived their patients utilized the device till the 'Last' puff thereby exposing the patients to the risk of PseudoAdherence and related complications.<sup>7</sup>

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 2. This often leads to suboptimal response with continued threat of Exacerbations or Symptoms of Dyspnea in patients with COPD 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 'Guess estimating' the content or volume of spray by Shake and Listening or Visualizing the actuation spray. Nearly ~70% pts continue to follow these 'Age-old practices' that are not approved, advocated or validated by any regulatory body including FDA.<sup>12</sup>

In a study by J.B. Connor et.al., 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.<sup>13</sup>

In an epidemiological survey conducted with 202 pulmonologists utilizing dose counter pMDI's, most patients (≥75%) were still perceived to be inhaling the device till the 'LAST' spray thereby exposing them to possible adverse outcomes of persistent asthma or exacerbations.<sup>7</sup>

The Adverse outcomes with Tail off include increased Exacerbation rate, Stress (physical or mental) related to treatment acquisition or referral to other specialty, QoL deterioration due to persistent day-or nighttime symptoms.

### Pseudoadherence: 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



**Fig. 3: Digital Dose Counter pMDI's**

'Right' quantity.<sup>14</sup> Similarly EMEA has recommended a mechanism to convey information on the 'Start point' of Tail off spray that should be provided with these devices.<sup>15</sup>

### Digital pMDIs: Defines Adherence... Prevents Pseudoadherence

Poor control of asthma symptoms is due in part to incorrect use of oral inhaler devices that deliver asthma medications, such as poor inhalation technique or use of a metered dose inhaler (MDI) after the recommended number of doses is expelled. Lack of a dose counter makes determining the number of remaining doses in an MDI problematic. National Asthma Education and Prevention Program (NAEPP) recommended that the only reliable method for determining the number of doses remaining in a canister is to subtract the number of doses used from the number available. In a study it was found that only 8% reported counting the actuations used.<sup>16</sup>

Until accurate dose counters Figure 3 are added to pMDIs, counting the number of doses administered is the only accurate method with which to tell when the canister should be discarded.<sup>11</sup>

In an epidemiological survey, it was found that Dose counter pMDI were suggested as a viable option to track adherence by 141 (70%) pulmonologists in most of these cases.<sup>7</sup>

In a study of patient satisfaction

with a pMDI including a dose counter, LaForce *et al* found that an integrated dose counter was an important contributor to patient satisfaction. They found 92% of subjects agreed the dose counter helped them track doses, and that 75% would recommend the inhaler to a friend.<sup>17</sup>

### Digital pMDIs: Treats 'Pseudo Severe Asthma'

The clinical impact of dose counter including digital pMDI was further reviewed by DUSS panel and they found that these devices offer significant improvement in the asthma status that has been poorly controlled.<sup>18</sup>

### 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 recommends use of pMDIs that offer Reliable information on 'Tail off' and 'Dosage delivered'. The addition of an 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 upon, as well as reducing the risk of patients taking a sub-therapeutic dose by using the inhaler past the label claimed number of doses.

Tracking Pseudoadherence Reliably and Accurately with Digital pMDIs 'Assures' Therapeutic Response to ICS/LABA.

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