

Nonadherence in Patients with Severe Asthma: Pandora's Box Is Open, but Still Full



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A relatively small proportion of patients with asthma have poor control and frequent exacerbations despite high-dose inhaled corticosteroids and long-acting β -agonist (ICS/LABA) treatment. Termed step 5 in the Global Initiative for Asthma (GINA) management strategy, evidence-based treatment options for these patients have rapidly evolved.¹ Principal among the new developments is a move away from long-term oral corticosteroids toward the highly effective, but costly biological agents.²

In practice, for most clinicians managing patients, the decision to add therapy is done through a symptom-based approach backed up with measures of lung function and airway inflammation.³ Navigating this management pathway requires great attention as it is recognized that there are several unique challenges among patients with severe asthma.⁴ One challenge is that some patients with asthma have another condition that has similar symptoms. For example, dyspnea related to exercise in obese and deconditioned asthmatics gives a false-positive signal when a clinician uses a symptom-based approach. For other patients, mastery of inhaler use is not possible and, when not recognized by a clinician, leads to escalation of therapy. Adherence to therapy is another consideration in deciding to advance treatment to step 5 therapy. During busy daily consultations, it can be challenging to assess medication adherence in an objective manner. Patients' self-reported adherence and clinicians' own estimation of patients' adherence are usually not very reliable. Digital technologies that assess adherence and inhaler technique can be used to quantify adherence and are of clinical value in promoting adherence through bio-feedback.⁵ However, there are relatively small numbers of these systems in use. To assess real-world, unbiased, population patterns of drug utilization, pharmacy dispensing data are among the most objective measures of medication adherence.

In this issue of the journal, van Boven et al⁶ report an important study in which the relationship between adherence to

ICS/LABA therapy and prescribing patterns of step 5 therapy was evaluated. Using pharmacy dispensing data via the Australia national government funding system, they performed a retrospective cohort study of people with asthma initiating ICS/LABA therapy. A 1-year preindex period to assess inclusion and exclusion criteria was followed by a 1-year postindex period to assess adherence trajectories and other predictors for additional GINA step 5 treatment. To obtain these trajectories, the authors made use of an innovative analytic clustering technique, called group-based trajectory modeling (GBTM).⁷ GBTM has not been used before to assess long-term asthma adherence. Notably, it does not simply provide a binary yes-no answer on whether patients are adherent or not. Yet, it rather groups patients by the actual pattern of drug refills over time. The primary outcome of their study was the percentage of patients initiating ICS/LABA who received additional GINA step 5 low-dose maintenance oral corticosteroids, asthma pathway-specific biologics, or antimuscarinic treatment during a follow-up time of 2 years after 1-year adherence assessment. Four distinct adherence trajectories were identified. Persistent users, termed "good adherers," represented only 1 in 10 of the population. In contrast, 1 in 5 of the cohort were "nonpersistent users." The majority of patients had a pattern of frequently skipping prescriptions. There was a small cohort who were termed "seasonal users," a particular feature of asthma reported in Australia. This description of different patterns of long-term adherence to ICS/LABA treatment is novel, and clinicians in practice should bear this in mind when they see poorly controlled patients and prescribe ICS/LABA treatment.

In the study, approximately 1 in 20 of patients progressed to step 5 therapy. Reassuringly, this relatively low rate of progression to step 5 treatment has also been reported from other database and registry studies.⁸ It is interesting to note that patients with good adherence had the highest likelihood of receiving additional step 5 therapy. Nonetheless, nonadherent patients represented over 80% of patients being prescribed additional step 5 therapies. This important finding highlights the importance of assessing, objectively, adherence to previously prescribed therapy before progressing to additional therapy. In unadjusted analyses, women, patients aged 40 to 44 years, and patients with anxiety were more likely to be prescribed an additional GINA-5 treatment. In a retrospective study, such as the one performed by van Boven, it is not possible to identify why people behaved in this manner. Furthermore, prospective research is required to understand the person-level factors.

The current GINA guideline and management strategy approach has been with us for some time. Although it seems logical and is easy to comprehend, there are several issues that are worthy of questioning. For example, the seemingly logical step of adding more treatment when somebody has not responded to

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their prior treatments should be questioned. Principally, asthma is a condition characterized by variable airflow obstruction, in other words a condition that generally comes and goes rather than one that progressively and inexorably progresses. Arguably, the absence of medication escalation in the intermittent or persistent non-adherence cohorts in the van Boven study suggests that the intermittent nature of the condition needs to be investigated in future research. Furthermore, the approach to promoting adherence in all people all the time is one that needs to be questioned. In its place a more subtle and dynamic approach to therapy, guided by objective measures of lung function and airway inflammation, will be the future of asthma treatment. The study reported in the journal by van Boven answers one question and nicely opens a Pandora's box of further important questions; for this the authors are to be congratulated and readers encouraged to consider taking the time to read this paper.

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