

SMART isn't

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In the mid-1980s, the respiratory community responded with surprising speed and consensus to identify the treatment factors most responsible for the phenomenon of rising asthma mortality. Overreliance on bronchodilator therapy had led to a crisis-oriented approach to care whereby symptoms were responded to rather than prevented.¹ Guidelines subsequently emphasized the early use of inhaled corticosteroids to quench underlying airways inflammation, thereby preventing symptoms and clinical instability.^{2,3} This widely adopted approach has been successful in reducing asthma mortality, and more recent guidelines have taught physicians to titrate their maintenance therapy to suppress all or nearly all day-to-day symptoms of asthma not only because this is intrinsically worthwhile to patients seeking to improve their quality of life but also because targeting good control reduces the likelihood of exacerbations and lung function lost to remodeling.⁴ In this issue of the Journal, Bateman et al⁵ report their extensive examination of the relationship between day-to-day symptoms and the risk of future exacerbations. Two findings from their study provide much needed support for the symptom prevention approach to care.

Asthma specialists might be surprised that there remains a need to prove that preventing symptoms is key to achieving best outcomes in asthma. It would seem, however, that primary care physicians remain unconvinced. We recently reported our largest survey of asthma control in the primary care setting, working with 354 physicians who used a simplified control questionnaire in more than 10,000 of their own patients to gauge current control status.⁶ Physicians often misclassified their uncontrolled patients as being controlled. When we looked closely at the phenomenon, the discrepancy was explained by excess quick reliever use. That is, primary care physicians were often willing to overlook excess bronchodilator need as a manifestation of poor disease control and a harbinger of subsequent clinical instability. The physicians' indifference to this signal notwithstanding, we found that poorly

controlled patients were twice as likely to require hospital care, 3 to 4 times as likely to seek emergency department care, and 6 times as likely to require an urgent office visit compared with the controlled patients. Bateman et al report comparable findings in their review of 12,584 patients with asthma taking various inhaled corticosteroid (ICS)-based regimens in 5 large clinical trials. The control achieved by each patient was categorized by using the current Global Initiative for Asthma criteria.⁷ That is, patients were considered controlled when they had (1) no nocturnal symptoms of asthma, (2) daytime symptoms of asthma no more than 2 days per week, (3) reliever use no more than 2 days per week and no more than 4 inhalations in total, (4) morning peak flow greater than 80% predicted, and (5) no activity limitations attributable to asthma. Patients who were not considered controlled were termed either partly controlled (if 1 or 2 of these criteria were not met) or uncontrolled (if 3 or more criteria were not met). Compared with the controlled patients, both suboptimally controlled groups were at increased risk of severe exacerbation compared with the controlled patients; the partly controlled patients were twice as likely to have an exacerbation, and the uncontrolled patients were 6 times as likely. These findings reaffirm the value of using day-to-day symptom frequency as a guide to titrate maintenance therapy. They should also prompt the Global Initiative for Asthma to re-examine its decision to parse suboptimal control into 2 arbitrary categories—partly controlled and uncontrolled—given that both states imply that a patient's risk of instability is high and that preventive therapy should be augmented.

The second major finding of the analysis by Bateman et al arises from the different maintenance regimens studied in the 5 clinical trials. The investigators examined the relationship between control and exacerbation risk not only in patients assigned to a conventional regimen of maintenance anti-inflammatory therapy and separate quick relief bronchodilator but also in patients who were treated with the novel single maintenance and reliever therapy (SMART) whereby patients use a low dose of scheduled ICS/long-acting β -agonist (LABA) maintenance therapy and the same medication as a quick reliever to treat breakthrough symptoms. Thus far, only the fixed dose combination of budesonide with formoterol has been used in this fashion. On reflection, SMART poses a conundrum to the thoughtful clinician. If patients are treated successfully by this regimen and enjoy symptom control (with a low likelihood of exacerbation), they will not need quick relief therapy, and SMART is indistinguishable from stable dosing with ICS/LABA maintenance therapy. Patients who use their maintenance inhaler frequently to relieve symptoms are by definition suboptimally controlled, and the strategy is unsuccessful. Presumably the SMART strategy either is intended to be a transitional dose-finding strategy or assumes that patients will settle into a narrow range of occasional quick-reliever need that does not disappear yet remains consistent with widely accepted criteria of adequate control. However, Bateman et al reveal that this hope for control is seldom achieved by the

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SMART strategy. Only 17.4% of SMART-treated patients were considered controlled; 38.3% were partly controlled (with 1 or 2 excess symptoms); and patients in the largest group, 44.3%, were uncontrolled, with 3 or more undesirable symptoms. The relationship between uncontrolled symptoms and the risk of exacerbation was qualitatively similar among all treatment regimens, but the relationship was not as strong among SMART-treated patients, suggesting that the control of day-to-day symptoms had become a less reliable predictor of important clinical outcomes. Severe exacerbations, although recorded less frequently in SMART-treated patients, occurred often enough to be a significant and ongoing concern. For example, in the largest of the SMART trials analyzed by Bateman et al, the whimsically named SMILE study, 1 in 7 SMART-treated patients had a severe exacerbation within a year of beginning the therapy.⁸

If asthma control is the exception rather than the rule with SMART and if severe exacerbations remain frequent, why have early adopters argued that SMART is a superior means of preventing exacerbations? The question of novelty aside, Cates and Lasserson⁹ noted in a recent Cochrane review of SMART that interpretation of many published studies is confounded by inadequate blinding when conventional ICS/LABA therapy as a comparator is administered via different compounds and inhalers from those used in the SMART therapy arm. Among the few adequately blinded trials (4 of the 5 analyzed by Bateman et al^{8,10-12}), patients receiving budesonide/formoterol SMART were compared either with patients treated with budesonide monotherapy or with patients using both budesonide and formoterol but in lower doses than the SMART-treated patients. Better outcomes with combination ICS/LABA therapy compared with ICS alone are not a novel or remarkable finding, nor is the better outcome seen with higher doses of maintenance therapy. The recent Cochrane review concluded that "... [SMART] has not been demonstrated to significantly reduce exacerbations in comparison with current best practice..."⁹

Do we have information on other future risks associated with SMART therapy? Bateman et al caution that their current analysis did not permit them to study longer-term outcomes such as lung function decline, but they did note that other monitoring techniques such as sputum eosinophil counts might provide valuable insights. Such insights were provided by a careful study reported by Pavord et al¹³ in the pages of the Journal last year. In a closely monitored cohort of SMART-treated patients, 1 year of single maintenance and reliever therapy was associated with significant increases in sputum and bronchial biopsy eosinophil counts compared with the same outcomes measured in patients treated with a conventional ICS/LABA regimen. Direct comparison between treatment arms is confounded by higher ICS doses given to patients in the conventional treatment arm, but if SMART therapy

outcomes are considered simply as change from baseline, biopsy eosinophil counts rose significantly over the treatment year.

After publication of the early SMART trial outcomes, I spoke to a primary care physician who was enthusiastic about the promise of this novel strategy. He regarded the use of SMART as a Trojan horse approach for his patients with difficult-to-treat asthma. Whenever they reached for a bronchodilator, he reasoned, they would receive an aliquot of inhaled anti-inflammatory therapy titrated to their obvious need. Compliance would not require education and persuasion but would become involuntary; the problem of symptom misperception was either left unconsidered or assumed to be trivial. The findings reported by Bateman et al should curb such enthusiasm. Despite the availability of newer medications and formulations, there is no evidence that we should abandon the life-saving strategy of symptom prevention to return to the previously discredited approach of symptom-driven care.

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