

Treatment adherence in asthmatic patients: The last frontier?

Eric D. Bateman, MD, FRCP Cape Town, South Africa

Key words: Asthma, inhalers, adherence

Recent classifications of severe asthma distinguish between difficult-to-treat or problematic asthma and treatment-refractory asthma.^{1,2} Much current research aims to identify the unmet need for additional treatments targeting phenotypes in which key mechanisms might play a role. Less attention is paid to problematic asthma, where issues relate to health systems and caregivers (lack of access to treatment or wrong diagnosis) and the behavior of patients, specifically poor adherence to asthma medications.

Research on patient adherence to asthma medications has been limited by imprecise measurement tools to estimate inhaler use.^{3,4} Although electronic monitors that measure adherence were developed more than 15 years ago, they are infrequently used.³ However, when combined with the facility to provide real-time feedback and reports, their routine use becomes an option. The recently developed Smartinhaler Tracker (Nexus6 Limited, Auckland, New Zealand) device, which, when clipped onto an inhaler, records each activation of the device and can be programmed to prompt patients to use their inhaler and provide reports to motivate adherence.^{4,5} Recent reports on the use of this device have provided valuable insights into patient behavior that should prompt a serious review of current strategies to improve adherence.⁵⁻⁷

Methods for ensuring adherence recommended in management guidelines focus mainly on improving the skills of health professionals to communicate and motivate patients, and some include aids to assist and encourage patients to take their medications.⁸ However, effecting behavior change, first among physicians and then in their patients, is difficult and time-consuming, and in general, published methods for achieving this are complex and impractical in the primary care setting because of time and other constraints.⁹ Thus the prospect of using patient-friendly technology is attractive.

The study by Foster et al¹⁰ in this issue of the *Journal* is both novel and ambitious. In a 2 × 2 randomized trial design with general practitioners as the unit of randomization, these investigators

attempted to compare the efficacy of 2 interventions administered alone or together compared with usual care. The first intervention involved audiovisual inhaler reminders from the electronic monitor up to twice daily when inhaler use was not recorded and adherence feedback (inhaler reminders and adherence feedback [IRF]). The second intervention involved a behavioral intervention: brief personalized discussion between the general practitioner and patient based on responses to a short questionnaire about inhaler use (personalized adherence discussions). Adherence among patients not randomized to IRF was monitored covertly. As expected, patients who received IRF (with or without personalized adherence discussions) had significantly better adherence overall and at 6 months than those who did not receive IRF, and although not statistically significant, those who received either 1 or both interventions had fewer severe exacerbations than those who received usual care. Thus the primary message of the study is that patient-friendly technology is superior to a behavioral approach in improving adherence. However, the results of this study, viewed alongside the findings of previous studies with this device, raise several other important issues.

These findings expose the reality gap between doctors' expectations and patients' behaviors and the poor performance of behavioral approaches. Usual general practitioner care, even after a refresher course on asthma care and with personalized adherence discussions, was associated with only 46% adherence over 6 months, which further decreased to only 29% at 6 months. Although in the IRF group these figures were better (73% over 6 months), adherence decreased to only 60% at 6 months, which is a relatively short horizon for long-term care. This was in a clinical setting, in which adherence rates are generally higher.

This raises several questions. Are these rates, rather than the 80% or higher required in clinical trials, acceptable? Is it not unrealistic to believe that more than a minority adhere to treatment to this extent? Should adherence alone be the goal, given that repetitious encouragement and scolding might impair the patient/doctor relationship? Poor adherence is clearly undesirable because a large proportion of patients have symptoms that remain suboptimally controlled. However, acceptance of this fact, and that poor adherence is endemic might be better than current practice, in which physicians, believing that the prescribed dose is being taken, are likely to overprescribe (increase the dose or add other medications), adding cost and potential for side effects, which introduce a further burden on the patient and erode adherence.

Other observations from studies with electronic monitoring have a bearing on this matter. First, patient reporting of inhaler use includes both overreporting and underreporting. Patel et al⁴ observed that underusers overreport inhaler use, whereas overusers underreport inhaler use. Whether this false reporting is unintentional or deliberate, it confirms that patients want to please (and adhere to what their physicians direct) but take liberties based on their own perceived need.

From the Division of Pulmonology, Department of Medicine, University of Cape Town.
Disclosure of potential conflict of interest: E. D. Bateman's institution has received funding from Boehringer Ingelheim, AstraZeneca, Almirall, Novartis, Merck, Takeda, Actelion, Aeras, Chiesi, Cephalon, Sanofi-Aventis, TEVA, and Glaxo SmithKline; he has received compensation for board membership and/or delivering lectures from AstraZeneca, Elevation Pharma, Napp Pharma, Novartis, Almirall, Forest, Merck, Takeda, GlaxoSmithKline, Chiesi, Nycomed, and Pfizer; and he has received consultancy fees from Navigant Consulting, the IMS Consulting Group, ALK-Abelló, Hoffmann la Roche, ICON, Actelion, Aeras, and Cephalon.

Received for publication August 6, 2014; accepted for publication August 8, 2014.

Corresponding author: Eric D. Bateman, MD, FRCP, University of Cape Town Lung Institute, George Street, Mowbray 7700, Cape Town, South Africa. E-mail: eric.bateman@uct.ac.za.

J Allergy Clin Immunol 2014;■■■:■■■-■■■.

0091-6749/\$36.00

© 2014 American Academy of Allergy, Asthma & Immunology

<http://dx.doi.org/10.1016/j.jaci.2014.08.004>

Second, they take matters into their own hands. In a 6-month clinical trial of twice-daily controller treatment monitored electronically, after some months, twice-daily therapy was taken on only 49% to 54% of days, but overall, patients took approximately 80% of the prescribed number of doses, suggesting use of additional treatment on some days, which compensated for underuse days.⁷

These findings, together with the current study, suggest that “regular treatment” is not regular in most patients and that maintenance treatment should be assumed in most patients to be intermittent and patient regulated. Thus the term “intentional nonadherence” should be reviewed and possibly be changed to “patient-adjusted maintenance therapy.” For some conditions, treatment might be symptom driven; in others it will be governed by other considerations. In a large study of determinants of intentional and unintentional nonadherence in 24,017 patients receiving maintenance treatment for a variety of chronic diseases, including asthma, medication beliefs/perceived need, concerns about safety of drugs, and affordability mediated unintentional nonadherence through intentional nonadherence.¹¹ The implications of revised terminology for maintenance treatment is that rather than expecting patients to adapt to an unrealistic regimen, perhaps treatment strategies should be designed to better fit normal human behavior. This is not peculiar to asthma but is the basis for promoting once-daily or even intermittent treatment for avoiding use of more than 1 treatment and for the use of depot injections for certain conditions. In asthmatic patients an example of symptom-driven adherence is the so-called single inhaler as maintenance and reliever therapy (SMART) approach, in which budesonide/formoterol is used as both maintenance and reliever treatment rather than as maintenance treatment with a short-acting β_2 -agonist serving as a reliever. In a recent study of the SMART approach versus usual regular maintenance treatment plus a short-acting β_2 -agonist, in which both groups were required to take twice-daily maintenance treatment, electronic monitoring confirmed that the number of days on which 1 and 2 doses of maintenance treatment were used was higher in the SMART group, suggesting that intentional nonadherence is not random but regulated by the patient’s perception of need (or lack of need).¹² Thus it is possible that the fall-off in adherence in the current study related to reduced perception of need because of improvements in clinical control observed in all study arms, a common phenomenon in clinical studies.⁹ To interrogate this, the adherence rate of each patient would have to be matched to their day-by-day clinical status rather than expressed as group mean effects.

Few would doubt that patients who follow the advice of their physicians and adhere to the treatments prescribed are likely to enjoy the best results. The study by Foster et al¹⁰ points to the fact that adherence can be improved with modern technology. However, this study, together with other studies that have accurately measured inhaler use, has exposed deficiencies in our concepts of adherence and points to a need for a broader view than simply counting doses. Customized patient-friendly treatment that anticipates and accommodates usual behavior and addresses conscious and unconscious medication beliefs is more likely to achieve the desired goal of disease control. Arguably, this, rather than the development of new drugs, should be viewed as the “last frontier” of asthma management.

REFERENCES

1. Bousquet J, Mantzouranis E, Cruz AA, Ait-Khaled N, Baena-Cagnani CE, Bleecker ER, et al. Uniform definition of asthma severity, control and exacerbations: document presented for the World Health Organisation consultation on severe asthma. *J Allergy Clin Immunol* 2010;126:926-38.
2. Chung KF, Wenzel SE, Brozek JL, Bush A, Castro M, Sterk P, et al. International ERS/ATS Guidelines on definition, evaluation and treatment of severe asthma. *Eur Respir J* 2014;43:343-73.
3. Berg J, Dunbar-Jacob J, Rohay J. Compliance with inhaled medications: the relationship between diary and electronic monitoring. *Ann Behav Med* 1998;20:36-8.
4. Patel M, Perrin K, Pritchard A, Williams M, Wijesinghe M, Weatherall M, et al. Accuracy of patient self-report as a measure of inhaled asthma medication use. *Respirology* 2013;18:546-52.
5. Foster JM, Smith L, Usherwood T, Sawyer SM, Rand CS, Reddel HK. The reliability and patient acceptability of the SmartTrack device: a new electronic monitor and reminder device for metered dose inhalers. *J Asthma* 2012;49:657-62.
6. Patel M, Pilcher J, Travers J, Perrin K, Shaw D, Black P, et al. Use of metered-dose inhaler electronic monitoring in a real-world asthma randomized controlled trial. *J Allergy Clin Immunol Pract* 2013;1:83-91.
7. Perrin K, Williams M, Wijesinghe M, James K, Weatherall M, Beasley R. Randomized controlled trial of adherence with single or combination inhaled corticosteroid/long-acting beta-agonist inhaler therapy in asthma. *J Allergy Clin Immunol* 2010;126:505-10.
8. Global Initiative for Asthma. Global strategy for asthma management and prevention 2014. Available at: www.ginasthma.org. Accessed May 2014.
9. Haynes RB, Ackloo E, Sahota N, McDonald HP, Yao X. Interventions for enhancing medication adherence. *Cochrane Database Syst Rev* 2008;(2):CD000011.
10. Foster JM, Usherwood T, Smith L, Sawyer SM, Xuan W, Rand CS, et al. Inhaler reminders improve adherence with controller treatment in primary care asthma patients. *J Allergy Clin Immunol* 2014;134:XXX-XXX.
11. Gadkari AS, McHorney CA. Unintentional non-adherence to chronic prescription medications: How unintentional is it really? *BMC Health Serv Res* 2012;12:98.
12. Patel M, Pilcher J, Pritchard A, Perrin K, Travers J, Shaw D, et al. Efficacy and safety of maintenance and reliever combination budesonide-formoterol inhaler in patients with asthma at risk of severe exacerbations: a randomised controlled trial. *Lancet Respir Med* 2013;1:32-42.