

Nonadherence to Asthma Treatment: Getting Unstuck



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NONADHERENCE IS OLD NEWS

Nonadherence in patients with respiratory diseases has been well documented. More than 25 years ago, clinical asthma researchers began to realize that patient self-reports of high rates of treatment adherence, including those produced through clinical trial diary cards, were largely fictional, exaggerating adherence by more than 50%.¹ Reports from studies using blood serum measures of adherence began to produce a sobering reality about the extent of the nonadherence problem, including documentation that a group of St Louis adolescents suffering fatal asthma episodes had subtherapeutic theophylline levels at the time of death.² Subsequently, 2 methodological breakthroughs brought about rapidly increased understanding of the breadth of the nonadherence problem. First, in 1990, a Denver engineering group produced an electronic tracking device for metered dose inhalers. The cottage industry of studies that followed revealed that half of prescribed controller medication was never taken by patients.³ Electronic tracking devices quickly became the criterion standard for measuring inhaler adherence, although high rates of device failure could bias finding⁴ and an unanticipated boost to adherence produced by awareness of the electronic tracking device may have unintentionally increased adherence.⁵ Second, access to large prescription refill databases produced an even more objective, large-scale view of medication-taking behavior.⁶ Remarkably, refill studies revealed that as many as 30% of prescriptions for controller medications were never filled,⁷ and 57% of patients obtaining an initial fill of inhaled corticosteroid/long-acting beta agonist medication did not return again within 12 months for a second fill.⁸ These facts began to portray a previously unrecognized complexity to the nonadherence problem not captured by simply examining average adherence rates while also pointing to one simple fact: most patients with persistent asthma take no controller medication on most days.

INTERVENTIONS ARE PROLIFIC BUT NO SILVER BULLET HAS ARRIVED

Recognition of the depth of the asthma nonadherence problem unleashed a flood of studies designed to improve adherence. Attempts to change patient behavior included dose

simplification,⁹ patient education,¹⁰ motivational interviewing,¹¹ adherence feedback,¹² provider communication skill training,¹³ and use of mobile communication technology.¹⁴ Collectively, most interventions had a positive but modest impact on adherence. Multifaceted interventions that combined these strategies were often more effective¹⁵ but were also resource intensive and therefore not easily disseminated to large and diverse clinical settings.

GETTING STUCK

The field of adherence research has become stuck. Despite widespread awareness of the problem of nonadherence and numerous randomized controlled trials testing adherence interventions, patients with asthma have not become more adherent over time. A sample of 9 studies conducted between 1996 and 2015 and using objective measures of adherence indicate no overall change in adherence rates over 3 decades (Table 1).

In addition, interventions to improve asthma treatment adherence, while prolific and innovative including leveraging mobile communication devices, have not had a widespread impact on the behavior of patients with asthma. A meta-analysis of randomized controlled trials to improve adherence in children with a chronic illness produced a median effect size of 0.49.²⁵ Although data from the meta-analysis in that report were presented in alphabetical order by author name, when portrayed by publication date from 1985 to 2012, no systematic upward trend of effectiveness over the 27-year-span emerges (Figure 1). In short, new strategies and improved adherence measures have not resulted in increased adherence.

GETTING UNSTUCK

The 10 articles included in this special issue provide new perspectives on an old problem with exploration of 4 areas of adherence research: (1) definitions and terminology, (2) research design and methods, (3) inhaler competency, and (4) patient-centered care. The articles reflect collaborations across 12 countries, with most from Europe. Six of the writing groups²⁶⁻³¹ have emerged from the European Respiratory Effectiveness Group (EREG) meeting in association with the 2015 European Asthma Allergy and Clinical Immunology Annual Congress; the article by Van Ganse and Price serves as the introduction to the other 5 EREG articles. These, along with the other 4 articles, produce the following insights:

1. Definitions and terminology. The Ascertaining Barriers to Compliance taxonomy, introduced by Vrijens et al²⁷ and referenced by other EREG authors, is intended to standardize adherence-related terminology for clinical and research use. By distinguishing adherence concepts temporally (initiation,

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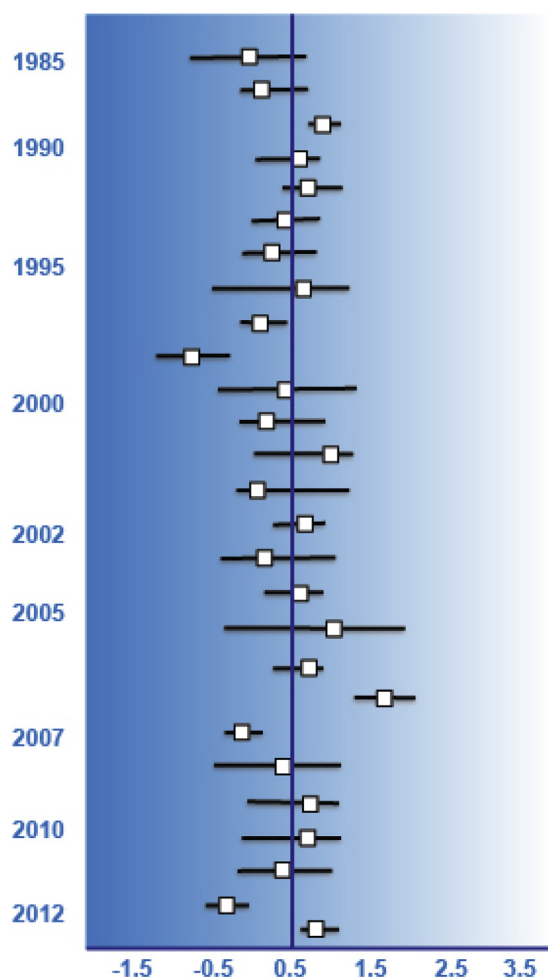
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TABLE 1. Average pediatric asthma adherence in studies using objective measures

Author	Year	Mean % adherence
Milgrom et al ¹⁶	1996	40
Chung and Naya ¹⁷	2000	64
Jonasson et al ¹⁸	2000	46.9
Bender et al ¹	2000	52
McQuaid et al ¹⁹	2003	48
Walders et al ²⁰	2005	46
Bender et al ²¹	2007	47
Krishnan et al ²²	2012	58
Mosnaim et al ²³	2015	19
Bender et al ²⁴	2015	36

**FIGURE 1.** Effect size of adherence interventions.

implementation, persistence), the taxonomy recognizes that understanding nonadherence involves more than simply examining the average of doses taken over time, and provides a framework for further investigation and intervention. The subsequent article by Dima et al²⁸ introduces the Asthma Care Model, which similarly outlines a prescription-to-outcomes path that tracks the sequence of treatment events from

diagnosis through treatment prescription, drug exposure, asthma trigger, and health outcomes. Both models provide new means of examining and understanding adherence.

2. Medication delivery technology. Discussions about non-adherence frequently start and end with examination of medication use. Dima et al²⁸ bring focus to the significant additional problem of inhaler nonadherence. Braido et al²⁹ emphasize that patients are unlikely to acquire inhaler competence if their provider lacks the knowledge and skill to give correct training. Providers may further inadvertently undermine inhaler adherence when patients are prescribed inhalers with different delivery systems (mixed platforms) or change inhaler devices (switching). Several pharmaceutical companies are currently developing a new generation of inhalers that deliver medication from a single platform and introduce technology capable of coaching proper inhaler use and improved adherence. It remains to be seen whether such technologies improve adherence in the population of asthma sufferers.
3. Research design and methods. Several of the articles emphasize the disconnect between clinical trial evidence and the “real world” of asthma management. Although not using the term *implementation research*, they nonetheless make a strong case for it. For example, Vrijens et al²⁷ cite the “gap between efficacy results derived from well-controlled, short-term RCTs involving highly selected populations and effectiveness evaluations conducted in more everyday, real-life settings, typically involving diverse patient populations, across a wide range of care setting and patients characteristic and evaluation over longer time intervals than are used in RCTs.” Braido et al²⁹ argue that randomized controlled trial studies often “...exclude many of the real-life factors that interact with idealized efficacy when therapies are used in the routine care environment, such as comorbid conditions...wide ranging lifestyle factors... and varying levels of treatment adherence.” Van Boven³¹ asserts that change must happen at the health care system level, including consideration of the potential adherence benefits of lowering co-pays and providing nontraditional health care delivery such as mobile health clinics. Furthermore, examination of system-level interventions must consider their cost-effectiveness. The report by Bender et al³² reintroduces the importance of using persistence as a primary dependent measure in “real-world,” nonclinical trial research where a surprisingly large number of patients abandon their treatment plan. The Laforest et al³³ article mines data from a large French database to show that early controller medication refill behavior following an initial prescription does not predict long-term adherence. Finally, Sulaiman³⁴ presents a unique adherence measurement methodology that uses audio recordings of patient inhalations to reveal inhaler errors that include inadequate flow, failure to inhale, exhalation into the inhaler, and multiple inhalations.
4. Patient-centered care. The international patient-centered care movement emphasizes the importance of effective provider-patient communication that includes sensitivity to individual patient differences, values, and preferences.³⁵ The importance of patient engagement is discussed by several writing groups. In their introduction to the set of EREG articles, the Van Ganse and Price²⁶ and Costello³⁰ writing groups highlight the large potential benefits to improved asthma management when providers use shared decision

making, a communication tool for delivery of patient-centered care.^{26,30} Other articles similarly emphasize components of shared decision making including providing adherence feedback,²⁸ checking inhaler satisfaction,²⁹ eliciting patient attitudes and beliefs,²⁹ seeking shared treatment goals,³¹ and assessing patient treatment preference.²⁷ Van Boven³¹ also make a case for the SIMPLES approach to effective patient engagement and treatment tailoring.

WHAT NEXT?

Adherence to asthma treatments is low and has not improved over the last 2 decades despite numerous attempts to create innovative behavioral interventions. The collection of reviews and reports included in this special issue deliver guidelines to help advance the adherence research field. These include recognizing that the problem of nonadherence stretches beyond the simple question of whether a patient took the correct amount of medication every day; that inadequate adherence and incorrect inhaler use characterize most patients with asthma and contribute to poor disease control; and that both need to be targeted as new interventions, medication delivery devices, and mobile communication tools appear in the marketplace. Although the traditional randomized controlled trial remains an essential research design for drug development, implementation research designs must be adopted to test delivery of interventions capable of cost-effectively impacting large numbers of patients to change adherence at a population level. Shared decision making is an effective communication tool that helps engage patients and tailor treatment plans on an individual level; it remains to be determined how to train large numbers of health care providers working in diverse clinical settings with significant time limitations to proficiently use it.

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