

## Current perspectives

# Adherence intervention research: What have we learned and what do we do next?

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Although there is general agreement from studies demonstrating that adherence to inhaled corticosteroid therapy is often inadequate to establish consistent control, relatively little concurrence exists in reports of interventions to correct the problem. Half of the studies reviewed found that the experimental intervention did not change adherence, and behavior change reported by patients was often not accompanied by changes in treatment success. Studies used a variety of methods that differed in quality with findings that were often contradictory. Key limitations in many studies included reliance on inadequate adherence measures, inclusion of convenience samples of well-motivated patients, and assessments of intervention outcomes artificially boosted by attrition of least adherent participants. Research is encouraged into innovative interventions that are brief, easily implemented, and can be tailored to individual patients and diverse clinical settings. Of particular importance is inclusion of hard-to-reach patients, including urban and rural poor and the use of valid measures of adherence at intervals sufficient to establish enduring benefit. (*J Allergy Clin Immunol* 2003;112:489-94.)

**Key words:** Adherence, intervention, asthma

The escalating burden of asthma has caused global concern over the past several decades. Research into the factors that account for this trend holds the keys to future medical and public health countermeasures. At present, the only recourse is to make the best use of approaches already known to reduce morbidity and mortality associated with this disease.<sup>1</sup> Asthma affects more than 15 million people in the United States. Inhaled steroids are safe and efficacious, but adherence to these medications is poor in all patient groups, including low-income and minority patients, who experience the most morbidity from asthma.<sup>2,3</sup> Imperfect adherence can contribute significantly to asthma morbidity and mortality. For children with asthma, the average medication adherence rate of 48% was determined by a meta-analysis of 10 stud-

ies.<sup>4</sup> Similar findings have been reported for adult patients.<sup>5</sup> Significant individual variation in adherence rates directly affects disease control. In a 3-month study of children with asthma, those who experienced an exacerbation had a median adherence with inhaled corticosteroid therapy of 14%, whereas those whose disease remained under control demonstrated a median adherence rate of 68%.<sup>6</sup> The wide-ranging disparity in adherence emphasizes the need to use reliable measures to distinguish between patients who adhere to the therapeutic regimen and those who do not, both in clinical practice and in research. Attention to adherence leads to improved patient management and more accurate interpretation of the results of clinical trials.

Although there is general agreement among studies describing poor adherence, there is relatively little concurrence in reports of interventions to correct the problem. Studies use a variety of methods that differ in quality, and their findings are often contradictory. Individual projects add to the literature base but rarely are definitive because of varying context and small sample size. Properly conducted research on interventions to improve adherence is necessary to inform clinical decisions in the treatment of asthma. This article provides a critical appraisal of recently published studies that address adherence and makes suggestions for future research that might help the physician make use of sound evidence for clinical decisions.

## INTERVENTION STUDIES HAVE ADDRESSED ADHERENCE

Numerous research efforts have been directed at improving adherence to asthma treatments. An adherence intervention is one in which a change in behavior is sought to increase adherence with medical or health provider advice.<sup>7</sup> A literature search for relevant intervention studies was executed using the MEDLINE, CINAHL, Psych-Info, ACP, Central, Coch, Dare, and Ipab databases from 1992 to the present. A total of 205 potential published reports was identified. The source literature population of studies consisted of controlled clinical trials in peer-reviewed journals that included educational or behavioral interventions with patients who had asthma and that used a measure of adherence. All reports not meeting these criteria were excluded. The bibliographies of reviewed

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papers were additionally surveyed for relevant reports. Sixteen published studies conforming to the selection criteria were identified and are summarized in Table I.

A variety of individual and group education interventions ranging from 1 to many sessions over periods up to 1 year comprised the programs. Many included written educational materials, and some were linked to the health care provider who in turn translated the information into a written, individualized action plan. A small number of studies included less-conventional behavior-change schemes, such as pharmacy-based instruction<sup>8,9</sup> and use of an electronic interactive device that transmitted daily information from the home of the patient to the caregiver's office.<sup>10</sup>

Seven studies reported no change in adherence or asthma control after interventions that often involved many hours of patient contact.<sup>9,11-16,17</sup> For example, 221 adults with asthma were randomly assigned into 1 of 3 groups: high intervention, low intervention, or usual care.<sup>11</sup> Despite receiving educational materials, a 1-hour individualized asthma education session, monthly support groups, and follow-up telephone calls from a health educator, the high intervention group was undifferentiated from the low intervention or usual care groups in medication use or measures of respiratory illness, health care use, or functional status. The authors hypothesized that, in light of successful behavior change in an earlier study, "usual care" had resulted in behavior change no different than that created by the educational intervention.

A similar lack of treatment effect was seen in 2 additional studies with relatively high-level interventions involving at least 6 hours of education.<sup>14,18</sup> Two studies reported improvement in medication adherence but not asthma control.<sup>19,20</sup> Absence of improvement was attributed to inadequate medical treatment<sup>19</sup> and failure of the educational intervention to motivate patients to change their behavior even though knowledge had increased.<sup>20</sup>

Nine studies reported significant change after educational intervention, including enhanced adherence and improved symptom control.<sup>10,14,19-25</sup> However, the measurement of both adherence and treatment outcome in most of these studies relied exclusively on patient self-report, a flawed method of outcome assessment.<sup>26,27</sup> Although several interventions demonstrate promise for broad implementation in clinical settings, overall limitations of the body of adherence intervention research requires careful review before establishing guidelines for future research.

#### **PUBLISHED INTERVENTION STUDIES DO NOT SEEM TO PROVIDE BENEFIT SUFFICIENT TO JUSTIFY THE RESOURCES THEY REQUIRE**

Many interventions involved a significant amount of professional time, yet few were very effective. In consideration of the positive selection bias operating in most studies as described in the following, the absence of behavior change resulting in better asthma control in these studies is striking. Reviewing adherence interventions

described in 34 citations with patients representing a variety of chronic conditions, including diabetes, rheumatoid arthritis, epilepsy, hypertension, chronic obstructive pulmonary disease, human immunodeficiency virus, schizophrenia, and asthma, McDonald and colleagues<sup>28</sup> found that only about half were effective in changing behavior, and even among these, self-reported behavior change was often not verified by objective measures. Effective interventions were more likely to be those involving combinations of strategies, such as providing counseling, reminders, reinforcement, and written information. However, effects were generally modest, leading the authors to conclude that in most cases costs outweighed benefits. Health care resources are limited, and little justification exists for expensive interventions that are not very effective and cannot reach the neediest populations.

#### **SELF-REPORTS USUALLY EXAGGERATE ADHERENCE**

Most studies used self-report to measure adherence, largely ignoring sizable literature establishing that patients greatly overreport adherence.<sup>6,26-28</sup> Seven of the 12 studies using self-reported measurement found improved adherence after the intervention. Absence of improvement was found in 2 of the remaining 4 studies in which adherence was assessed by returned canister weight<sup>13</sup> or electronic peak flow meter.<sup>12</sup> In 2 studies, electronically recorded peak flow meter use actually decreased over the course of the study, despite educational interventions<sup>12,29</sup>; one found that patient reports of treatment adherence increased.<sup>29</sup> Interestingly, inaccuracy of self-report also might explain the absence of improved outcomes in the face of apparently increased adherence.<sup>19,20</sup> Two studies conducted by the same group, 1 measuring adherence by self-report and the other by canister weight, produced strikingly different outcomes; self-reported adherence improved dramatically,<sup>22</sup> whereas canister weight adherence evaluations revealed no difference between education intervention and control groups.<sup>13</sup> Many patients desire to provide answers that earn the approval of the person asking the question. Under this social desirability effect,<sup>30</sup> the discrepancy between actual and reported behavior increases as the authority figure is viewed with increasing regard by the respondent. Patients who participate in educational interventions might wish to please study staff by reporting the behavior changes that the staff are clearly invested in documenting. In short, the impact of adherence interventions in some cases might be limited to changing what patients report without actually changing their behavior.

#### **STUDIES MAY EXCLUDE PATIENTS WITH POOR ADHERENCE**

Studies include only patients who are willing to volunteer. Those patients who are inconsistent users of health care (ie, those who are most in need of an adher-

TABLE I. Randomized adherence intervention studies meeting criteria for inclusion

| Reference                              | Patient Characteristics |             |                  |                            | Intervention                                                                                                                                                                                                                |                   |                               |                                                                                                                                                                                          | Adherence                                                        |                         |
|----------------------------------------|-------------------------|-------------|------------------|----------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------|-------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------|-------------------------|
|                                        | Total Sample (IG)       | Age (years) | % Minority       | Dropouts Total sample (IG) | Protocol                                                                                                                                                                                                                    | Duration (Months) | Assessment Intervals (months) | Outcome                                                                                                                                                                                  | Measure                                                          | Outcome                 |
| Allen RM, et al, 1995 <sup>16</sup>    | 116 (58)                | 18 - 65     | 7                | 3 (2)                      | 4 weekly 2.5 hr ES                                                                                                                                                                                                          | 1.5               | 0, 3, 6, 9, 12                | I: knowledge<br>ND: spirometry, peak flows, symptoms, unscheduled visits, medical treatment                                                                                              | SR                                                               | I                       |
| Bailey WC et al, 1999 <sup>11</sup>    | 232 (78, 78)            | Adults      | 33               | NI                         | High intervention: self-help workbook, individualized counseling, monthly asthma support groups<br>Low intervention: less contact, no support group                                                                         | 2                 | 6, 12, 18, 24                 | ND: use of health services, symptoms, functional status, respiratory illnesses (all improved)                                                                                            | SR                                                               | ND                      |
| Bonner S et al, 2002 <sup>20</sup>     | 119 (56)                | 4 - 19      | 96               | 19 (6)                     | Family intervention: Asthma diaries, 3 monthly group ES, phone calls on diary use and communication with MD<br>MD Intervention: Family Coordinator accompanied subjects on visit to MD & encouraged use of AP, PFM, diaries | 3                 | 0, 3                          | I: asthma symptoms, activity limitations, knowledge, self-regulation                                                                                                                     | Family: SR<br>MD: anti-inflammatory prescription, responsiveness | Family: I<br>MD: I      |
| Burkhart PV et al, 2002 <sup>12</sup>  | 42 (21)                 | 7 - 11      | 2                | 0                          | Contracting, reinforcement, tailoring, reminders                                                                                                                                                                            | 1.2               | 12                            | NI                                                                                                                                                                                       | Electronic monitoring of PFM                                     | Declined in both groups |
| Cote J et al, 1997 <sup>13</sup>       | 188 (95)                | ≥ 16        | NI (Canada)      | 39 (NI)                    | ES & Self-Management Group based on PFM or on symptoms                                                                                                                                                                      | 12                | 12 before and 12 after        | I: knowledge<br>ND: hospitalizations, ED visits, steroid courses, days lost from work/school                                                                                             | Canister weight                                                  | ND                      |
| Cote J et al, 2001 <sup>21</sup>       | 126 (63)                | ≥ 18        | NI (Canada)      | 28 (2)                     | Limited intervention: AP from their physician<br>Structured intervention: AP plus formal structured ES emphasizing self-management                                                                                          | 12                | 0, 6, 12                      | Improved peak flows, knowledge, self-management, quality of life at 12 months                                                                                                            | SR                                                               | I                       |
| Couturaud F et al, 2002 <sup>19</sup>  | 72 (36)                 | 18 - 72     | NI (France)      | 18 (NI)                    | Six 30-60 minute ES, and an AP which was reviewed and adjusted at each follow-up visit                                                                                                                                      | 12                | 0, 1, 3, 6, 9, 12             | I: self-management at 12 months<br>ND: symptom-free days, change in FEV1, quality of life, knowledge<br>W: oral steroid intake                                                           | SR                                                               | I                       |
| Gallefoss F et al, 1999 <sup>14</sup>  | 78 (39)                 | 18 - 70     | NI (Norway)      | 16 (3)                     | Two 2-hour group ES, 1-2 individual ES, brochure, and treatment plan                                                                                                                                                        | 12                | 0, 12                         | ND: steroid courses, rescue medications dispensed                                                                                                                                        | Medication dispensing records from pharmacy                      | I                       |
| Garrett J et al, 1994 <sup>15</sup>    | 500 (251)               | 2 - 55      | 29 (New Zealand) | 49 (23)                    | Individualized ES and AP                                                                                                                                                                                                    | 9                 | 0 - 9                         | I: night awakenings for asthma<br>ND: hospital admissions, ED visits, days lost of school/work, urgent care visits                                                                       | SR, physician report                                             | ND                      |
| Guendelman S et al, 2002 <sup>10</sup> | 134 (66)                | 8 - 16      | 76               | 7                          | The Health Buddy, an interactive disease-monitoring device, asked about symptoms and management, gave praise, encouragement, and asthma facts; Information from the Health Buddy was transmitted to study nurses            | 3                 | 0, 1.5, 3                     | I: less activity limitation, fewer hospitalizations, less symptoms, improved peak flow readings<br>ND: symptoms, sleep disturbance, ED visits, hospitalizations                          | SR, Health Buddy report                                          | I                       |
| Kotes H et al, 1995 <sup>22</sup>      | 85 (NI)                 | 27 - 70     | NI               | 9 (NI)                     | 7 weekly 90-minute sessions about asthma self-management or a Wait-list control group                                                                                                                                       | 2                 | 0, 6, 12                      | I: fewer asthma attacks, physician visits, less medication use, improved cognition, better self-management                                                                               | SR                                                               | ND                      |
| Levy ML et al, 2000 <sup>21</sup>      | 211 (103)               | ≥ 18        | (UK)             | 32 (20)                    | 3 ES with a nurse, totaling 2 hours (only 77% of IG patients attended at least one session)                                                                                                                                 | 4.5               | 0, 3, 6                       | I: By subject report, more ICS use, higher peak flows, fewer routine visits to physician<br>ND: hospitalizations, number of severe attacks, days missed from work, uncontrolled episodes | SR                                                               | I                       |
| Lopez-Vina A et al, 2000 <sup>24</sup> | 150 (NI)                | 17 - 65     | (Spain)          | 50 (NI)                    | Individual asthma education and self-management plan based on peak flow readings compared to asthma education self-management based on symptoms.                                                                            | 12                | 0, 0.5, 1, 3, 6, 9, 12        | I: FVC, % predicted<br>ND: symptoms, sleep disturbance, absenteeism school/work, ED visits hospitalizations                                                                              | SR                                                               | I                       |
| Turner MO et al, 1998 <sup>16</sup>    | 117 (53)                | 18 - 55     | 10 (Canada)      | 25 (9)                     | ES, AP, training in use of PFM, and self-management in 7 semi-yearly sessions. Patients in the control group managed their asthma based on symptoms.                                                                        | 6                 | 0, 1, 2, 3, 4, 5, 6           | ND: FEV1, symptoms, PC20 methacholine, quality of life improved in both groups                                                                                                           | SR                                                               | ND                      |
| Weinburger M et al, 2002 <sup>2</sup>  | 1113 (447)              | ≥ 18        | 20               | 215 (NI)                   | Pharmacists provided ES, and PFM training<br>Control groups received either PFM or usual care                                                                                                                               | 12                | 0, 6, 12                      | ND: between pharmaceutical care and peak flow monitored group on adherence, quality of life, hospitalizations or ED; Pharmaceutical care group had more ED visits and hospitalizations   | SR                                                               | ND                      |
| Wilson SR et al, 1993 <sup>14</sup>    | 323                     | 18 - 50     | NI               | 45 (NI)                    | 45-minute group or individual ES over 4 sessions;<br>Control groups received either education booklet or no intervention                                                                                                    | 4                 | 0, 12, 24                     | I: environmental control in both E groups; Less symptoms, reduced hospitalization at 1 and 2 yrs in both E groups                                                                        | MDI technique                                                    | I                       |

AP = Action plan, ES = Education session, I = Improved over comparison group, ICS = inhaled corticosteroids, IG = Intervention Group, ND = No difference between intervention and comparison group, PFM = peak flow meter, SR = Self-report, W = Worse than comparison group.

**TABLE II.** Recommendations for research on interventions to improve adherence

|             |                                                                                                                                                                                                                                              |
|-------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Content     |                                                                                                                                                                                                                                              |
| 1.          | Identify the root causes of poor adherence (eg, family and social obligations or distractions, inability to obtain medications or refills, poor provider-patient communication, fear of side effects, distrust of the medical establishment) |
| 2.          | Focus on the groups most at risk for a poor treatment outcome, including vulnerable groups such as low-income, minority, adolescent, and elderly patients                                                                                    |
| 3.          | Develop interventions that are simple and easily applicable to the clinical setting                                                                                                                                                          |
| 4.          | Address not only patient behavior but also the provider and the provider-patient relationship                                                                                                                                                |
| 5.          | Address prevention of the decay of adherence over time                                                                                                                                                                                       |
| Methodology |                                                                                                                                                                                                                                              |
| 6.          | Identify inexpensive, reliable technology to measure adherence                                                                                                                                                                               |
| 7.          | Include as outcomes not only adherence but also disease-focused and patient-focused outcomes such as change in FEV <sub>1</sub> and quality of life                                                                                          |
| 8.          | Target interventions to include the most poorly adherent patients                                                                                                                                                                            |
| 9.          | Consider new research designs more acceptable to patients (eg, tailored interventions, alternatives to randomized clinical trials but also those that use individualized, tailored interventions)                                            |
| 10.         | Include adherence measures in trials of treatment effectiveness                                                                                                                                                                              |

ence intervention) do not typically enter research studies. Adolescents with diabetes who agree to participate in studies have higher rates of adherence than those who do not.<sup>31</sup> Thus, from the onset, most of the educational intervention studies are biased by inclusion of relatively motivated and cooperative patients.<sup>28</sup> Few studies in [Table I](#) targeted those at greatest risk for poor adherence and poor asthma control such as inner-city, low-income, minority patients. A limited number of studies have addressed behavior change in such high-risk populations.<sup>10,23,25,32-34</sup>

Study dropouts are often less adherent than those who remain in the study.<sup>35</sup> Hence, exclusion of these patients further increases positive selection bias. Half of the studies in [Table I](#) lost at least 25% of participants. By omitting those patients least likely to be adherent, the overall adherence of the group is artificially enhanced. The combined effects of studying only people willing to volunteer for studies, reporting results only for those who complete the program, and relying on patient report of adherence behavior significantly increases the likelihood of showing an exaggerated adherence outcome.

## GUIDELINES FOR FUTURE ADHERENCE INTERVENTION RESEARCH

Although many efforts have been directed at creating interventions to enhance treatment adherence and improve disease outcomes, no cost-effective, easily implemented, and disseminated program able to target difficult-to-reach patients has been established. The need for methodologically sound studies of innovative approaches to adherence promotion is evident. As with all clinical trials, such studies should include randomized assignment to treatment, equal treatment across groups aside from the experimental treatment, and follow-up that includes appropriate end points at intervals sufficient to establish enduring benefit. Following are specific considerations for new content and methodology to guide adherence research ([Table II](#)).

## CREATE NEW STRATEGIES FOR IMPROVING ADHERENCE

Creating new strategies for improving adherence must start with efforts to identify root causes of undertreatment, particularly in minority populations. Recent surveys have established that medication adherence is particularly problematic among low-income and minority patients with asthma.<sup>27,36,37</sup> African-American patients might not trust their health care provider or the medications they prescribe. Qualitative research such as focus groups allows the investigator into the personal world of the patient to increase understanding of the complex set of medical, emotional, and social experiences underlying patient behavior.<sup>38</sup> Such explorations bring to light the feeling and beliefs that determine how asthma medical care is seen by the individual patient and increase ability to tailor interventions to particular patient groups.

New interventions must be simple, easily implemented, and applicable in many clinical settings. A meta-analysis on adherence intervention studies across diseases concluded that few were effective but noted that the simple intervention of recalling patients who missed appointments was one of the most cost effective.<sup>7</sup> Another relatively efficient intervention consisting of mailing information to patients before a scheduled visit to inform them of what to expect during the visit reduced nonattendance at a diabetes clinic from 15% to 4.6%.<sup>39</sup> Initial investigations using home asthma telemonitoring demonstrates potential for exchange of information between patient and health caregiver office and encouragement of maintenance of self-management behaviors.<sup>10,40</sup> Pharmacy-based interventions have the advantage of easily reaching a large number of patients. More frequent physician contact in the first 6 weeks of treatment for depression resulted in higher adherence rates.<sup>41</sup> Helping physicians to follow practice guidelines, to develop communication and motivation skills, to maintain cultural sensitivity, and to appreciate the diverse health beliefs of patients might be one of the best means of reaching a

large number of patients during routine contact with health caregivers.<sup>33,34,42</sup> Patients are more adherent when they have contact with their physician<sup>43</sup> and when they know their adherence is being monitored.<sup>44</sup> Physicians who received this training spent less time per patient than those without the training, and their patients demonstrated better asthma control.<sup>35</sup> Finally, the study described by Bonner et al<sup>21</sup> was one of the few successful interventions that illustrates the possible usefulness of the use of a combination of simple interventions and also in targeting not only patients but simultaneously their families and their provider. The ongoing challenge will be to continue to identify low-cost interventions administered in the clinical setting where the patient obtains health care that promotes better treatment adherence.

### ADOPT STRONG RESEARCH METHODS

This review has established that adherence-intervention research must move away from studies that include only convenience samples of motivated patients and target those whose adherence is often most discrepant with guidelines and for whom the consequences of nonadherence might be most damaging. Studies that target hard-to-reach patient populations, such as the urban and rural poor, might ultimately bring the greatest benefit by improving attempts to reverse trends of increased morbidity and mortality in these groups.

Proof of benefit can be established only with accurate adherence measures and inclusion of disease outcome end points. Self-report of adherence, whether by diary card, questionnaire, or interview, is inadequate to evaluate behavior change. A need therefore exists for reliable and low-cost methods for adherence measurement. Several electronic devices that record use of inhaled asthma medications have been pressed into service,<sup>45</sup> but none is marketed for use with dry powder inhalers. Difficulties of producing such devices include Food and Drug Administration requirements and the multiple delivery systems incorporated into newer medications. Behavior change is an important objective but alone is inadequate to establish benefit from an adherence intervention. Improved disease control, as reflected in decreased  $\beta_2$ -agonist use, symptom days, oral steroid prescriptions, emergency department visits, and hospitalizations, should follow interventions that accurately document significant improvement in adherence behavior.

Improvement in adherence by patients and the use of best available evidence by physicians are needed to diminish the intolerably high morbidity and mortality associated with asthma. There is no single solution that will improve adherence in all patients. The best treatment strategies include those that are brief, easily implemented, and can be tailored to individual patients and diverse clinical settings. More comprehensive interventions targeting both patients and health caregivers demonstrate promise but require further objective evaluation. The patient-physician relationship is central to the improvement of patient adherence. Medications are becoming

ever more effective, and adherence affects all self-administered therapy, thus progress in this area of health care delivery holds promise for elevating the care of our patients and the practice of medicine.

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