Determinants of Patient Adherence to an Aerosol Regimen

Joseph L Rau PhD RRT FAARC

Introduction
Compliance or Adherence?
Defining Adherence
Types of Nonadherence
Measurement of Adherence With Aerosol Regimens
General Studies of Adherence With Aerosol Therapy
Correct Aerosol Device Technique
Complexity of Inhalation Regimen
Dosing Frequency
Combination Formulations of Inhaled Drugs
Route of Administration: Oral vs Aerosol
Type of Inhaled Medication: Inhaled Corticosteroids vs β2 Agonists
Patient Awareness of Monitoring and Effect of Feedback on Monitoring
Patient Beliefs, Sociocultural, and Psychological Factors
Summary: Improving Adherence With Aerosol Therapy

Patient adherence with prescribed inhaled therapy is related to morbidity and mortality. The terms “compliance” and “adherence” are used in the literature to describe agreement between prescribed medication and patient practice, with “adherence” implying active patient participation. Patient adherence with inhaled medication can be perfect, good, adequate, poor, or nonexistent, although criteria for such levels are not standardized and may vary from one study to another. Generally, nonadherence can be classified into unintentional (not understood) or intentional (understood but not followed). Failing to understand correct use of an inhaler exemplifies unintentional nonadherence, while refusing to take medication for fear of adverse effects constitutes intentional nonadherence. There are various measures of adherence, including biochemical monitoring of subjects, electronic or mechanical device monitors, direct observation of patients, medical/pharmacy records, counting remaining doses, clinician judgment, and patient self-report or diaries. The methods cited are in order of more to less objective, although even electronic monitoring can be prone to patient deception. Adherence is notoriously higher when determined by patient self-report, compared to electronic monitors. A general lack of adherence with inhaled medications has been documented in studies, and adherence declines over time, even with return clinic visits. Lack of correct aerosol-device use is a particular type of nonadherence, and clinician knowledge of correct use has been shown to be imperfect. Other factors related to patient adherence include the complexity of the inhalation regimen (dosing frequency, number of drugs), route of administration (oral vs inhaled), type of inhaled agent (corticosteroid adherence is worse than with short-acting β2 agonists), patient awareness of monitoring, as well as a variety of patient beliefs and sociocultural and psychological factors. Good communication skills among clinicians and patient education about inhaled medications are central to improving adherence. Key words: compliance, adherence, aerosol, metered-dose inhaler, MDI, dry powder inhaler, DPI. [Respir Care 2005;50(10):1346–1356. © 2005 Daedalus Enterprises]
Introduction

The importance of patient adherence to prescribed medication therapy lies in the documented relationship of poor adherence to increased morbidity and even mortality.1–3 Baun et al found significantly worse asthma morbidity among children when they or their caregivers scored high on measures of nonadherence with therapy.2 Williams et al found that adherence to inhaled corticosteroid therapy, based on medical/pharmacy records, was approximately 50% in a large group of asthmatics, and negatively correlated with the number of emergency department visits.3 They also reported that each 25% increase in the proportion of time without inhaled corticosteroid medication resulted in a doubling of the rate of asthma-related hospitalization. Milgrom et al found that median compliance with inhaled corticosteroids among asthmatic children was 13.7% for those having exacerbations and 68.2% for those who did not.4

Compliance or Adherence?

There are 2 terms used in the literature to refer to how well a patient follows a prescribed regimen of drug dosing or any prescribed therapy: adherence and compliance. The latter term seems to be favored more recently in the literature, and this may be because of differences in the exact meaning of the 2 terms. While both terms describe agreement between a patient’s actions and prescribed therapy, “compliance” has the connotation of giving in to a request or demand; “adherence” on the other hand connotes staying attached or staying firm in supporting or approving, or demand; “adherence” on the other hand connotes staying attached or staying firm in supporting or approving, based on definitions in a standard Webster’s dictionary.5

“Adherence” thereby seems to imply a patient’s choice to follow prescribed therapy, while “compliance” implies a certain passivity to another’s request. In fact a synonym for “compliant” in one dictionary consulted is “obedient.”6 In a 1995 publication, Tashkin defined compliance “simply as following the instructions of the health-care provider.”7 As a result, “compliance” conjures a view of the patient as a passive participant following orders. In contrast, “adherence” describes an active patient who is an empowered partner in his or her care.8 Aside from political correctness, it seems to make sense to have a patient who actively desires to work with a health-care provider instead of one who follows directions with little interest in taking responsibility for the process. In an editorial accompanying a study on patient compliance, Mellins and associates commented that “there is a growing recognition that to improve significantly the way in which they use medicines and otherwise manage disease, patients must be actively involved in the process of determining the therapeutic plan.”9 Throughout this review, the terms “compliance” and “adherence” will correspond to those used in the particular studies described. Otherwise the term “adherence” will be used to describe agreement between prescription and practice.

Defining Adherence

Rand and Wise define “adherence” as “the degree to which patient behaviors coincide with the clinical recommendations of health-care providers.”10 They note that this definition is too broad and call for adherence to be situationally defined, with good adherence explicitly delineated. They also note that there is no gold standard for “good” or “acceptable” adherence. For example, adequate adherence may describe asthma-clinic patients who use 40% of the prescribed medication and are symptom-free and controlled. However, a subject in a research study who takes 60% of prescribed doses may be considered nonadherent.11 An example of the type of definition of adherence called for by Rand and Wise can be found in the context of a study by Tashkin et al, who used metered-dose inhaler (MDI) canister-weight criteria to define compliance ratings.12 For example, using calculated grams of medication per day, > 0.45 g/d might be “over-compliance,” 0.35–0.45 g/d “good compliance,” and so forth. Such a method gives a specific criterion (g/d) to rate degrees of compliance.

Types of Nonadherence

Nonadherence with therapy takes multiple forms, ranging from incomplete to total nonuse. The various types of nonadherence with prescribed therapy can be broadly categorized into 2 types: unintentional (not understood), and intentional (understood but not followed).13 Table 1 gives a more detailed outline of potential factors that can predispose to these types of nonadherence.11–13 Unintentional nonadherence includes misunderstanding the prescribed regimen, incorrect aerosol device technique, or language barriers. Intentional nonadherence can be caused by patient beliefs (eg, that drug therapy is ineffective, unnecessary, or dangerous), forgetfulness, stress, busy lifestyle, or complex, demanding aerosol regimens. Of the two, unintentional nonadherence may be easier to remedy.

Joseph L Rau PhD RRT FAARC, RRT FAARC is Professor Emeritus, Cardiopulmonary Care Sciences, Georgia State University, Atlanta, Georgia.

Joseph L Rau PhD RRT FAARC presented a version of this article at the 36th Respiratory Care Journal Conference, Metered-Dose Inhalers and Dry Powder Inhalers in Aerosol Therapy, held April 29 through May 1, 2005, in Los Cabos, Mexico.

Correspondence: Joseph L Rau PhD RRT FAARC, 2734 Livsey Trail, Tucker GA 30084. E-mail: joerau@comcast.net.
Measurement of Adherence With Aerosol Regimens

There are a number of methods for measuring congruence of patient behavior with prescribed aerosol therapy, which are listed in Table 2.9,11 These methods differ substantially in the degree of accuracy and objectivity with which patient adherence can be determined. In general, direct measures of patient behavior, such as direct observation or electronic inhaler monitors, give more accurate, valid measures than indirect methods such as patient diaries, self-report, or clinician’s judgment.9,11,14 There are several electronic monitors that have been reported in the literature for use with MDIs or dry powder inhalers (DPIs).

The “nebulizer chronolog” device and the “Doser Clinical Trials” device have been used with MDIs.15–17 The nebulizer chronolog is a microprocessor device built into the sleeve housing an MDI; it records the date and time of each inhaler actuation, by activation of a microswitch.4,15 The Doser Clinical Trials device is described as an inexpensive pressure-activated device, also used with MDIs.17 It is a round, flat device secured to the top of the MDI canister, and it records only the number of daily uses over a period of 45 days.18 A similar MDI electromechanical counter was reported by Yeung et al.19 The Electronic Diskhaler allows monitoring of the Diskhaler DPI, by recording drug blister piercing and airflow through the inhaler.20 A similar device, the Turbohaler Inhalation Computer has been used with the Turbohaler DPI, known as the Turbohaler in the United States.13 An electronic adherence monitor has also been reported for the Diskus DPI.21 It should be noted that not all electronic monitors guarantee actual inhalation of medication by patients. With the nebulizer chronolog, medication can be sprayed into the air, or the switch flicked manually. The Electronic Diskhaler records both blister perforation and airflow, which gives some indication that inhalation occurred following DPI loading.20

Tashkin et al investigated adherence with aerosol therapy, using the nebulizer chronolog, in comparison with canister weighing and patient self-report with a group of patients with chronic obstructive pulmonary disease (COPD).10 Their study found that both canister weights and self-report overestimated adherence with prescribed therapy among patients who were not informed of the nebulizer chronolog’s recording ability (Fig. 1).

Rand et al also used the nebulizer chronolog to compare adherence to a 3-times-daily use of 2 MDI inhalations of ipratropium or placebo by patient self-report at follow-up and canister-weight-change over a 4-month period.15 Both self-report and canister-weighing overestimated correct inhaler use, compared to nebulizer chronolog measures. Nebulizer chronolog data showed that only 15% of the subjects used the MDI an average of 2.5 or more times per day, as prescribed. In contrast, 73% of subjects self-reported correct daily inhaler use. Canister-weighing overestimated correct inhaler use as prescribed for 61% of participants, correctly estimated use for 39% (although not always as prescribed), and underestimated use for 0%. Nebulizer chronolog data also showed that 14% of subjects actuated their inhalers more than 100 times in a 3-hour interval, often before clinic visits, a practice known as “dumping,” or the “parking lot phenomenon.”9,15 Canister weighing cannot differentiate correct use from wasted medication.

Milgrom et al also looked at patient compliance to both β2 agonists and inhaled corticosteroids, using the nebulizer chronolog versus patient diaries.4 Figure 2 shows a summary of the compliance data for both inhaled medications over 13 weeks. Diary reports claimed a median use of β2 agonists of 78.2% of prescribed dose, and a steroid use of 95.4%. Data from the nebulizer chronolog giving time-corrected compliance (doses taken within the correct time window) showed 48% for β2 agonists and 32% for inhaled steroids. Only β2 agonists taken on a fixed schedule (2 or 3 times a day or every 6 hours) were included in the analysis. Similar results for electronic monitors in comparison with patient reports, canister weight, and remaining dose counts have been reported in other studies.18,22–23 A study by Burrows et al showed that patient self-reporting also overestimated adherence when compared to data from pharmacy-dispensing records for nebulized dornase alfa in cystic fibrosis patients.24 Based on the comparisons cited, it is relevant to note that results of different studies can depend at least partly on which measure of aerosol adherence is employed.
General Studies of Adherence With Aerosol Therapy

The general lack of adherence with prescribed aerosol therapy has been documented in a number of studies, including patients with asthma,\textsuperscript{25–27} as well as COPD.\textsuperscript{15,28–29} Rand and associates documented that COPD patients had poor adherence with prescribed 3-times-daily MDI therapy, as measured with the nebulizer chronolog.\textsuperscript{15} Fewer than 20% of 70 patients used their MDIs an average of 2.5–3 times per day as instructed, although almost 95% reported correct use as prescribed. Jönasson et al found a decline in adherence with twice-daily inhaled budesonide and placebo in mildly asthmatic children over a 27-month period of monitoring remaining doses with Turbuhaler DPIs.\textsuperscript{25} A disturbing finding from Mawhinney et al was that only 1 subject out of 34 in a clinical trial of 2 nonbronchodilator anti-asthma drugs (cromolyn-like and corticosteroid agents) was compliant with prescribed use, as measured with a nebulizer chronolog for MDI.\textsuperscript{27} Such findings raise questions about the validity of clinical trials, when patient medication use is thought to be best.

![Fig. 1. Percentage of adherence with prescribed metered-dose inhaler (MDI) medication among patients with chronic obstructive pulmonary disease, determined with 3 methods of monitoring: nebulizer chronolog (electronic MDI monitor), MDI canister weight change, and patient self-report. (Based on data from Reference 10.)](image-url)

Table 2. Methods of Measuring Adherence With Prescribed Aerosol Drug Therapy, Based On Measures Noted in the Literature\textsuperscript{*}

<table>
<thead>
<tr>
<th>Method</th>
<th>Example</th>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biochemical measures</td>
<td>Analysis of blood, urine, or secretions to measure drug level</td>
<td>Accurate</td>
<td>Expensive</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Objective</td>
<td>Intrusive, Limited drug tests, Limited recent drug therapy</td>
</tr>
<tr>
<td>Medication/device monitors</td>
<td>Electronic monitor records date and time of inhaler use</td>
<td>Accurate</td>
<td>Cannot tell if patient actually received dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Objective</td>
<td>Expensive</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Possible alteration of patient habits?</td>
</tr>
<tr>
<td>Observation of device technique</td>
<td>Direct review of patient performance with aerosol device, usually periodic</td>
<td>Accurate with training of observer</td>
<td>Limited to time of observation, Limited to device-use only, not dose schedule</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Simple</td>
<td>Requires staff time</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Objectively based</td>
<td></td>
</tr>
<tr>
<td>Medical/pharmacy records</td>
<td>Retrospective review of patient records or refills</td>
<td>Objective</td>
<td>Time required to obtain patient data</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Relatively simple to obtain</td>
<td>Limited to detecting nonrefills, No information on correct patient use or scheduling of drug with refills</td>
</tr>
<tr>
<td>Monitoring remaining dose counts or medication</td>
<td>MDI canister weighing, DPI doses left, SVN doses or solution packages left</td>
<td>Simple</td>
<td>Possible patient deceit by wasting doses</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Objective</td>
<td>No information on actual dosing schedule</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Low cost</td>
<td>Requires staff time</td>
</tr>
<tr>
<td>Clinical judgment of provider</td>
<td>Global judgment of health-care provider during clinic visits</td>
<td>Quick</td>
<td>Low validity and reliability\textsuperscript{14}</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Low cost</td>
<td></td>
</tr>
<tr>
<td>Patient self-report</td>
<td>Periodic recall survey or interview, Patient diary</td>
<td>Fast for health-care provider</td>
<td>Vulnerable to patient error or deceit\textsuperscript{15}</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Low cost</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ease of use</td>
<td></td>
</tr>
</tbody>
</table>

\textsuperscript{*}The methods are listed in order of relative accuracy, from greater to less. (Adapted from References 9 and 11.)

MDI = metered-dose inhaler

DPI = dry powder inhaler

SVN = small-volume nebulizer
Correct Aerosol Device Technique

Lack of adherence to aerosol therapy can be due to lack of understanding correct aerosol device or drug use, and was termed “unintentional” nonadherence in Table 1. Farber et al found that 23% of parents (n = 131) misunderstood the role of their asthmatic child’s inhaled anti-inflammatory medication, believing that it was for treatment of symptoms after they occurred, not for prevention. This was associated with decreased adherence to its daily use.12 A number of studies have documented problems patients have using aerosol devices and common patient errors, particularly with MDIs.30–34 While “press and breathe” seems simple when using an MDI, many patients lack the coordination for the split-second timing required between actuating the MDI and beginning a slow inhalation.31 Suboptimal therapeutic response and poor control of airway disease can result from faulty technique.31,35 Problems with patient use of aerosol devices can be worsened by inadequate knowledge of correct device use among health-care professionals. A study by Hanania et al of medical personnel’s knowledge of MDIs, MDIs with spacers, and a DPI had a mean ± SD knowledge score of 67 ± 5% for respiratory therapists, 48 ± 7% for house staff physicians, and 39 ± 7% for registered nurses.36 A similar study of the same types of aerosol devices found that pharmacists lacked adequate knowledge to properly instruct patients in inhaler use.37 DPIs can remove the need for hand-breath coordination with MDIs (a common problem) because DPIs are breath-actuated. However, a recent study by Melani et al found similar percentages of poor patient use with MDIs, compared to DPIs.38 In their study, 24% of patients used MDIs poorly; failure to correctly perform essential steps with the Aerolizer, Turbuhaler, and Diskus was 17%, 23%, and 24%, respectively. Use of a large-volume spacer reduced poor MDI use from 24% to only 3% of patients.

Complexity of Inhalation Regimen

The complexity of an inhalation regimen in managing airway disease can depend on the frequency with which an inhaled medication must be taken, the number of medications to be taken, and whether different types of aerosol devices must be used (eg, a nebulizer for one drug and a DPI for another).

Dosing Frequency

Medication adherence has been linked to the frequency with which a drug must be taken, for both oral and inhaled-drug regimens. Eisen et al used electronically monitored pill containers to measure patient adherence with antihypertensive medication.39 Their study found that adherence improved from 59% with a 3-times daily regimen to 83.6% with a once-daily regimen. Similarly, Cramer et al found the mean (SD) adherence rate for oral antiepileptic drugs was 87% (11), 81% (17), 77% (12), and 39% (24) for daily, twice-a-day, 3-times-a-day, and every-6-hours dosing, respectively, using an electronic pill bottle dispensing system.40 Prescribed frequency of drug use similarly affects inhaled medications. Coutts et al performed a pilot trial of the nebulizer chronolog to study compliance with inhaled prophylactic medication (corticosteroids) in children.16 Table 3 gives the results of their study for twice-a-day, 3-times-a-day, and every-6-hours dosing frequencies, with patient self-report and nebulizer chronolog monitoring data. A “compliant day” was defined as one with the correct number of puffs at appropriate times. As reported for oral medications, compliance declined with increasing frequency of use. Mann et al assigned patients to 2 groups, with group A taking 4 inhalations of flun-
combination. Correct use was 8 inhalations per day, for either group. Both groups had a run-in period with 4 inhalations twice-a-day. Compliance did not change for group A (twice-a-day dosing) from the run-in period. The percentage of days with less than 8 inhalations for group B increased from 20.2 ± 40.3% during the run-in, to 57.1 ± 49.6% with the change to every-6-hours dosing. The mean number of daily inhalations in group B decreased from 7.9 ± 2.5% to 6.8 ± 3.1% (p < 0.01) between the 2 time periods.

Combination Formulations of Inhaled Drugs

Combining 2 inhaled drugs into one formulation for inhalation could theoretically halve the number of times needed for drug administration, and thereby reduce the complexity for drug inhalation. Bosley et al reported a study in 1994 that compared separate inhalation of a corticosteroid (budesonide) and a short-acting β2 agonist (terbutaline) to a combination formulation of the two. All drugs were given using the Turbuhaler DPI and were to be taken twice daily. Adherence was monitored electronically with the Turbuhaler Inhalation Computer. When the 2 drugs were inhaled separately, compliance was similar for both the β2 agonist and the corticosteroid, at about 60–70%. This was somewhat surprising, since compliance with inhaled corticosteroid therapy is often thought to be poor, and worse than with bronchodilators. In addition, compliance was no better in patients using the combined formulation. These results may have been due to use of a short-acting β2 agonist, which requires more frequent use per day than a long-acting agent.

A study by Stoloff et al compared medication-refill persistence with (1) the corticosteroid fluticasone propionate and the long-acting β2 agonist salmeterol in combination in a single inhaler; (2) fluticasone propionate and salmeterol inhaled separately from 2 inhalers; (3) fluticasone propionate and montelukast taken together (inhaled, oral); and (4) fluticasone propionate and montelukast each taken singly as monotherapy. The cohort that used fluticasone plus salmeterol from a single inhaler had significantly better adherence (4.06 refills per 12-month period) than the other cohorts that used fluticasone (2.35 refills per 12-month period in the group that inhaled fluticasone and salmeterol from separate inhalers; 1.83 refills per 12-month period in the group that used fluticasone plus montelukast; and 2.27 refills per 12-month period in the group that used fluticasone alone). The combination formulation (fluticasone plus salmeterol in one inhaler) had refill persistence similar to that of the oral leukotriene modifier montelukast taken alone (4.51 refills per 12-month period), although montelukast monotherapy had the highest refill persistence.

The difference in results between the study by Bosley et al, with a short-acting bronchodilator, and that of Stoloff et al, with a long-acting bronchodilator, may well be due to the frequency of administration. In addition, the simplest form of drug therapy in the Stoloff et al study was oral montelukast taken as monotherapy, which had the highest adherence. The recommended dosage for montelukast is once daily, taken as a pill.

Route of Administration: Oral Versus Aerosol

Taking a dose of medication as a pill is reasonably simple and quick, assuming normal swallowing ability and consciousness. In terms of time needed for a dose, the MDI and DPI are closest among the various aerosol devices to pill-taking, although the multiple steps needed for correct use of either (MDI: shaking, exhaling, actuating, slow inhalation, and breath-hold; DPI: multi-step preparation, breath-hold) certainly requires a minute or more. In terms of simplicity, I would argue that a pill taken orally is far simpler than MDI or DPI use.

Kelloway et al used medical records together with pharmacy claims data to measure the compliance of patients prescribed oral theophylline and inhaled medications. All subjects used oral theophylline; 97% used inhaled corticosteroids and 8.4% used inhaled cromolyn sodium, with 5% taking both inhaled cromolyn and inhaled steroids. Both theophylline and inhaled corticosteroid dosing regimens ranged between 2 and 3 times daily. Cromolyn is usually prescribed on a 4-times-daily basis. As shown in Figure 3, the highest compliance was with oral theophylline (79% ± 34%), with inhaled corticosteroid and cromolyn at 54% ± 43% and 44% ± 34%, respectively. Since only a few patients had 2 inhaled formulations, the data from Kelloway et al suggest better adherence with oral drugs than with inhaled drugs. Compliance for oral theophylline was similar when patients were stratified into age groups of 12–17 years versus 18–65 years. Inhaled corticosteroid compliance was 30% in the younger group and 57% in the
older group, indicating an age difference in that particular study.

Table 4 summarizes results from the study by Kelloway et al,45 together with other studies46–49 that compared patient adherence with oral versus inhaled drug therapy.

Unfortunately, the studies listed in Table 4 all include inhaled therapy that must be taken multiple times daily. With the exception of the study by Kelloway et al, in which theophylline was prescribed, all of the other studies examined use of leukotriene modifiers, and most of these were the once-daily montelukast taken orally. Thus, there is some confounding of results between route of administration (oral vs inhaled) and frequency of dosing, with higher frequency of dosing for the inhaled drugs.

**Type of Inhaled Medication: Inhaled Corticosteroids Versus β2 Agonists**

There is a perception among clinicians that patient adherence with prescribed inhaled corticosteroids is worse than with inhaled β2 agonists. This has been attributed to the absence of immediate relief or perceptible effect from inhaled corticosteroids, compared to short-acting β2 agonists.43 A 2000 literature review by Cochrane et al of compliance with inhaled corticosteroids noted that studies have shown that patients took the recommended dose on 20–73% of days.50 Bosley et al compared a combination corticosteroid and β2 agonist inhaled formulation with separate delivery and found no difference in compliance when the 2 drugs were taken separately.42 At least 2 other studies have measured differences in adherence with inhaled corticosteroids and β2 agonists. Milgrom et al measured adherence of children with asthma to regimens of both inhaled corticosteroids and β2 agonists, using the MDI chronolog (also termed the nebulizer chronolog monitor).4 They found that doses taken within the correct time window, as prescribed (the “time-corrected compliance”), were 48% for β2 agonists and 32% for inhaled corticosteroids. Median days without medication were 20.4% for β2 agonists and 24.4% for inhaled steroids. They noted that 25% of patients did not take inhaled corticosteroids on more than 60% of the days studied.

Bender et al also found better adherence with β2 agonists than with inhaled corticosteroids.51 The results of their study are shown in Figure 4. The studies by Milgrom et al and Bender et al both support the view that inhaled corticosteroid adherence appears to be worse than adherence with inhaled β2 agonists. It should be noted that in both studies the β2 agonists were probably short-acting, as opposed to long-acting, although the specific drugs were not identified. Since inhaled corticosteroids and short-acting β2 agonists were both prescribed multiple times daily, it would not seem that the poorer results with inhaled corticosteroids were due to frequency of dosing. It is not clear if similar results would be found if adherence with inhaled corticosteroids were compared to long-acting β2 agonists.

**Patient Awareness of Monitoring and Effect of Feedback On Monitoring**

Studies of patient adherence with inhaled medications have found that informing patients that they are being
monitored for correct drug use improves adherence. Tashkin et al found that COPD patients who were uninformed of the nebulizer chronolog’s function had a 54% compliance rate, whereas a feedback group who was told of the nebulizer chronolog’s function had a 78% compliance with 3-times-daily MDI therapy. Nides et al divided COPD patients into a control group (n = 89) and a feedback group (n = 116). Actual adherence with prescribed MDI use 3-times-daily was monitored with the nebulizer chronolog. Patients in the control group were told only that the nebulizer chronolog’s function had a 54% compliance rate, whereas a feedback group who was told of the device’s recording ability did so. Dumping episodes usually occurred shortly before a clinic follow-up visit.

**Fig. 5.** Comparison of feedback and control groups on measures of adherence with metered-dose inhalers prescribed 3 times daily, among patients with chronic obstructive pulmonary disease. = percentage who averaged 2 sets per day. Days Adherent = mean ± SD percent adherent days. Taken as Prescribed = mean ± SD percent of total actuations taken as prescribed. (Based on data from Reference 52.)

In addition to the explicit factors such as understanding device use and instructions, complexity of inhalation regimen, and giving patients feedback on adherence, adherence can be influenced by a number of personal factors. These include health beliefs, such as need for medication, severity of disease, and risks of adverse effects, and sociocultural and psychological factors. Table 5 summarizes results from studies that examined the association of such factors with adherence to inhaled medications. There are some discrepancies among the studies. For example, Bosley et al found no association of socioeconomic status with adherence, whereas 2 studies by Apter et al found the reverse. Similarly, Horne and Weinman found that educational experience had no association with adherence, but the studies by Apter et al found this was associated with adherence. It may be that sample size and other sample factors explain the different findings. Variability in the relationship of age to adherence may be explained by different age groups in different studies. Horne and Weinman found that, among adults, older age had a positive association with adherence. McQuaid et al found that older age had a negative association in a sample of children age 8–17 years. Jónasson et al divided a sample of children age 7–16 years into 7–9 years and 10–16 years, and found that the older group had lower adherence than the younger group. A study by Labrecque et al reviewed pharmacy claims to investigate the effect of age on appropriate use of short-acting β₂ agonists among asthma patients. They also found higher appropriate use among the younger patients (age 5–15 years) than among 15–45-year-old patients.

The effect of patient education and self-management programs on corticosteroid use has been examined. Gallefoss and Bakke implemented an education program for asthma and COPD patients that consisted of a patient brochure, two 2-hour group-education sessions, individual sessions with a nurse or physiotherapist, and a treatment plan, with a control and treatment group. They found that steroid inhaler compliance measured from pharmacy records improved among asthmatics, from 32% among the controls to 57% among the program participants, which is almost a doubling. Among the COPD subjects, steroid inhaler compliance was 58% among the controls and 50% among the program participants, and education seemed to have little effect. However, in the educated group, among
both asthma and COPD patients, the amount of rescue short-acting β2 agonist dispensed was approximately half of that dispensed by the controls. A similar study with asthmatics by van der Palen et al investigated the effect of four 90-min education sessions and written guidelines on adjusting inhaled medication plans.20 They found that mean compliance improved from 83% (20–81 years old) in the run-in period to 92% (92 ± 52%) after education. However, compliance with an adjustment to the inhaled medications (specifically, doubling the inhaled steroid dose) was only 65% (233–244). Some patients increased inhalations by only 1 or 2 puffs. The patients were willing to more or less increase the dose but were apprehensive about doubling the steroid dose, which was perceived as too high.20

**Summary: Improving Adherence With Aerosol Therapy**

The multiplicity of factors that affect adherence with inhaled aerosol medications makes it difficult to suggest

<table>
<thead>
<tr>
<th>First Author, Year</th>
<th>Sample</th>
<th>Negative Association</th>
<th>No Association</th>
<th>Positive Association</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apter 199853</td>
<td>Asthma Adults &lt; 12 years formal education</td>
<td>Asthma severity</td>
<td>No variables found</td>
<td></td>
</tr>
<tr>
<td></td>
<td>n = 50</td>
<td>Poor patient-clinician communication</td>
<td>Locus of control measure</td>
<td></td>
</tr>
<tr>
<td></td>
<td>46±14 years old</td>
<td>Income &lt; $20,000</td>
<td>Attitude toward inhaled corticosteroids</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(20–81 years old)</td>
<td>Spanish as first language</td>
<td>Minority status</td>
<td></td>
</tr>
<tr>
<td>Apter 200354</td>
<td>Asthma Adults African-American ethnicity</td>
<td>No variables found</td>
<td>Favorable attitude toward inhaled corticosteroids</td>
<td></td>
</tr>
<tr>
<td></td>
<td>n = 85</td>
<td>Lower educational achievement</td>
<td>No variables found</td>
<td></td>
</tr>
<tr>
<td></td>
<td>47 ± 15 years old</td>
<td>Lower income</td>
<td>Favorable attitude toward inhaled corticosteroids</td>
<td></td>
</tr>
<tr>
<td>Bender 199851</td>
<td>Asthma Children Lower level of asthma knowledge</td>
<td>Child behavior disorder</td>
<td>No variables found</td>
<td></td>
</tr>
<tr>
<td></td>
<td>n = 24</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>6–12 years old</td>
<td>Family dysfunction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bosley 199513</td>
<td>Asthma Adults Depression</td>
<td>Anxiety</td>
<td>No variables found</td>
<td></td>
</tr>
<tr>
<td></td>
<td>n = 102</td>
<td>Interpersonal problems</td>
<td>Active participation in clinical decisions</td>
<td></td>
</tr>
<tr>
<td></td>
<td>18–70 years old</td>
<td>Gender</td>
<td>Asthma is a serious problem</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Age</td>
<td>Recent hospitalization for asthma</td>
<td></td>
</tr>
<tr>
<td>Chambers 199955</td>
<td>Asthma Adults Belief that inhaled corticosteroids were unnecessary if asymptomatic</td>
<td>No variables found</td>
<td>Active participation in clinical decisions</td>
<td></td>
</tr>
<tr>
<td></td>
<td>n = 394</td>
<td>Concern over adverse effects</td>
<td>Asthma is a serious problem</td>
<td></td>
</tr>
<tr>
<td></td>
<td>18–49 years old</td>
<td></td>
<td>Recent hospitalization for asthma</td>
<td></td>
</tr>
<tr>
<td>Horne 199956</td>
<td>Asthma (n = 78) others Concern over dependence</td>
<td>Gender</td>
<td>Higher necessity scores</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Adults</td>
<td>Long-term effects</td>
<td>Educational experience</td>
<td></td>
</tr>
<tr>
<td></td>
<td>n = 324</td>
<td>Number of prescribed medications</td>
<td>Asthma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>45.5 ± 18.3 years old</td>
<td></td>
<td>Older age</td>
<td></td>
</tr>
<tr>
<td>Labrecque 200358</td>
<td>Asthma Adults and children Age group 15–45 years old (older age)</td>
<td>No variables found</td>
<td>No variables found</td>
<td></td>
</tr>
<tr>
<td></td>
<td>n = 1,616</td>
<td>No variables found</td>
<td>No variables found</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5–45 years old</td>
<td>No variables found</td>
<td>No variables found</td>
<td></td>
</tr>
<tr>
<td>McQuaid 200357</td>
<td>Asthma Children Older age</td>
<td>Knowledge of asthma</td>
<td>No variables found</td>
<td></td>
</tr>
<tr>
<td></td>
<td>n = 106</td>
<td>Minority status</td>
<td>Responsibility for asthma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>8–16 years old</td>
<td>Morbidity</td>
<td>Reasoning about asthma</td>
<td></td>
</tr>
</tbody>
</table>

Table 5. Summary of Studies on the Effects of Health Beliefs; Demographics; Psychological, Sociocultural, and Socioeconomic Factors on Adherence With Aerosol Therapy
simple remedies. Improving adherence is made more difficult by the fact that health-care providers do not know if patients are adherent without the use of monitoring, preferably using some type of electronic monitor that can record the date and time of aerosol use. This would require additional clinician and staff time and expense, and is not practical for office and clinic practices. Table 6 lists recommended actions, based on the factors cited in this review, that evidence suggests are amenable to intervention. Lewis and Fink pointed out that the preparation of health-care professionals should emphasize the concept of partnership with patients to increase adherence. Patient education is a key component in partnering with patients. Health-care providers must be able to help the patient understand the disease and begin to master self-management skills. Patient education can also address and attempt to correct patient beliefs that can decrease adherence, such as beliefs about the need for the medication and concern over adverse effects and dependence. With good communication skills, health-care providers may be better able to identify problems with adherence, identify reasons for nonadherence, and seek appropriate solutions.

Table 6. Suggested Actions to Improve Patient Adherence With Inhaled Aerosol Medication Therapy

| Adequately prepared health-care provider |
| Knowledge of inhaler function and correct use |
| Understand concept of partnership with patient |
| Ability to communicate with patient |
| Recognition of patient barriers to adherence (language, cognitive, psychological) |
| Seek appropriate social service or psychiatric support for nonadherent patients when needed |
| Evaluate and review patient inhaler technique at initial and follow-up visits |
| Provide written treatment plan, specifying actions and times |
| Simplified aerosol-dosing regimen to extent possible and appropriate |
| Use of daily or twice-daily medications (eg, long-acting β2 agonists or tiotropium) |
| Use of combination aerosol formulations (eg, salmeterol plus fluticasone [Advair]) |
| Educate the patient about the effectiveness, use, function, and adverse effects of inhaled medications, especially corticosteroids |
| Give patients realistic expectations about medication effectiveness |
| Educate the patient about the severity of the disease and the risks of not using the medication |
| Use pulmonary function tests to document severity, effectiveness |
| Identify problems with patient’s medication expense |
| Is there a lower cost alternative? |
| Seek assistance programs from pharmaceutical companies |

(COMPILTED FROM REFERENCES 11, 60, AND 61.)

REFERENCES

21. Bogen D, Apter AJ. Adherence logger for a dry powder inhaler: a practical for office and clinic practices. Table 6 lists recommended actions, based on the factors cited in this review, that evidence suggests are amenable to intervention. Lewis and Fink pointed out that the preparation of health-care professionals should emphasize the concept of partnership with patients to increase adherence. Patient education is a key component in partnering with patients. Health-care providers must be able to help the patient understand the disease and begin to master self-management skills. Patient education can also address and attempt to correct patient beliefs that can decrease adherence, such as beliefs about the need for the medication and concern over adverse effects and dependence. With good communication skills, health-care providers may be better able to identify problems with adherence, identify reasons for nonadherence, and seek appropriate solutions.
60. Rubin BK. What does it mean when a patient says, “My asthma medication is not working”? Chest 2004;126(3):972–981.
Discussion

Rubin: I think it would be useful if we could modify those electronic monitors to shock patients when they forget to take their medication on time. Adherence is better if it involves a consequence, if it is easy, and if it is immediate. Adherence is much better for medications like oral contraceptives, with which there is a fairly immediate consequence if doses are missed.

Rau: I like the shocking monitor idea. This is a tough nut to crack. It’s true, we don’t have any really positive feedback measures to give patients, particularly in the case of inhaled corticosteroid. If they use it correctly, they probably won’t show up in the emergency department as soon, or they don’t end up being hospitalized, but that’s really the stick, not the carrot.

I think the best that we can do is educate patients about the risk of not using the drug, so that they realistically appreciate the risk. A little bit of shock therapy helps if they end up in the emergency department or get admitted, which sometimes scares people into better adherence. But, short of that, I did not find any perfect answer to the lack of patient adherence, which is probably around 50% across all medications and in the various studies. So I think education is the best we can do, and it may be the most costly, because who has time in a busy clinical setting to really work with the patient? And yet that is probably what is needed, and perhaps a lot of the lack of adherence is because we don’t work with the patient one-on-one because of the cost.

Atkins: This is a tough nut to crack. It’s often difficult to get a patient to use a medication. A Diskus inhaler should be used up once a month, but we see refill rates of only 4 or 5 a year, so adherence seems to be less than 50%. Most of the data is not about intervention. I think there has to be an intervention, be it a stick or a carrot.

One of the things GlaxoSmithKline tried in Scandinavia, where a lot of people have cell phones, was a simple reminder using the cell phone text-messaging system. In a text message they simply asked, “Did you take your medication?” As I recall, it appeared to improve compliance by 30 or 40 percent [unpublished data]. Are there other kinds of information or systems that might improve compliance?

Rubin: I know there are questions about this, but currently there is a penalty, called a co-pay, if you refill your prescription every month. If they use it less frequently than prescribed, they save money. Is there a way to provide financial benefits for patients to fill their prescription when they should, instead of penalizing them?

Atkins: That relates to a comment you made earlier about fluticasone. I suspect another point was the fact that a lot of people were getting a higher-dose prescription of fluticasone and then probably only using one MDI puff, because that makes it so they only have to fill the prescription every 2 months.

Nikander:* We have a prototype Adaptive Aerosol Delivery nebulizer system that monitors adherence and whether the parents used the device as instructed (ie, compliance with device instructions). We called the combined function of adherence and compliance “true adherence.” Feedback on how to use the device seemed to be important to the parents.1

Rau: That is a very good comment. The data from Nides and colleagues1 clearly showed better adherence among patients who knew they were being monitored and received feedback.

REFERENCE


Newman: You stressed the importance of involving patients in treatment plans. What about choice of inhaler device? Do patients adhere better if they’re using devices they prefer and helped choose?

Rau: That’s an extremely relevant question. I did not show any data on the effect of patient preference on adherence, and perhaps I missed some things in my literature search, but I didn’t see a lot of data on that. I think we tend to forget about patient preference, particularly in the American clinical setting. We instead look at the disease. What device/drug combination is available to treat that disease? And then we make the choice from that “Chinese menu,” to use Dick Ahrens’ analogy. We never asked the patient if they liked the device, though we don’t always have much choice about the device, particularly now. But I suspect that has something to do with it.

Pierson:† I want to make a comment as someone who manages patients with COPD, most of whom are elderly and many of whom have comorbidities that interfere further with the adherence that you’ve discussed. If I have a patient with severe COPD, according to the current GOLD guide-

———

* Kurt Nikander, Respironics, Cedar Grove, New Jersey.

† David J Pierson MD FAARC, Division of Pulmonary and Critical Care Medicine, Harborview Medical Center, University of Washington, Seattle, Washington.

REFERENCE

days of the railroad industry, before they had a standard railway gauge, and a train from one railroad system couldn’t go on the tracks of another railroad system. That didn’t help the traveler who needed to get from New York to Chicago.

It’s a complicated issue, but I think it would be good if, instead of 3 different breathing patterns for MDI, nebulizer, and DPI, and all the sub-differences, we had one standard breathing pattern and at least some type of standardization among the aerosol devices, so that patients heard similar instructions for MDI and DPI. Currently, we have to instruct the patient to breathe in totally opposite ways, which is very confusing.

Pierson: Or at least if they were using 2 different forms of dry powder drug, they could get both drugs from the same inhaler, or at least the same kind of inhaler that operates the same way.

Leach: In the early 1990s the Food and Drug Administration asked us for a dose-response study on QVAR. We decided that the only way to do it was to have patients come in 5 days a week for observation and training. And, as cited in the Busse et al study, we found a very significant dose-response relationship. Our assumption was that in past studies no one had forced patients to be that compliant. With some new drugs that are not quite as safe but are very effective, we have to find ways to make sure people are compliant in the clinical trials.

REFERENCE

Rau: I’m going to get on my “soap box” for a moment. Though I don’t have any quantitative data to support this, I think that an undesirable effect of the numerous new and improved aerosol technologies is that we’ve now got far too many choices of devices and too many differences among the device categories. It’s akin to the early days of the railroad industry, before they had a standard railway gauge, and a train from one railroad system couldn’t go on the tracks of another railroad system. That didn’t help the traveler who needed to get from New York to Chicago.

It’s a complicated issue, but I think it would be good if, instead of 3 different breathing patterns for MDI, nebulizer, and DPI, and all the sub-differences, we had one standard breathing pattern and at least some type of standardization among the aerosol devices, so that patients heard similar instructions for MDI and DPI. Currently, we have to instruct the patient to breathe in totally opposite ways, which is very confusing.

Pierson: Or at least if they were using 2 different forms of dry powder drug, they could get both drugs from the same inhaler, or at least the same kind of inhaler that operates the same way.

Leach: In the early 1990s the Food and Drug Administration asked us for a dose-response study on QVAR. We decided that the only way to do it was to have patients come in 5 days a week for observation and training. And, as cited in the Busse et al study, we found a very significant dose-response relationship. Our assumption was that in past studies no one had forced patients to be that compliant. With some new drugs that are not quite as safe but are very effective, we have to find ways to make sure people are compliant in the clinical trials.

REFERENCE

Rau: I’m going to get on my “soap box” for a moment. Though I don’t have any quantitative data to support this, I think that an undesirable effect of the numerous new and improved aerosol technologies is that we’ve now got far too many choices of devices and too many differences among the device categories. It’s akin to the early days of the railroad industry, before they had a standard railway gauge, and a train from one railroad system couldn’t go on the tracks of another railroad system. That didn’t help the traveler who needed to get from New York to Chicago.

It’s a complicated issue, but I think it would be good if, instead of 3 different breathing patterns for MDI, nebulizer, and DPI, and all the sub-differences, we had one standard breathing pattern and at least some type of standardization among the aerosol devices, so that patients heard similar instructions for MDI and DPI. Currently, we have to instruct the patient to breathe in totally opposite ways, which is very confusing.

Pierson: Or at least if they were using 2 different forms of dry powder drug, they could get both drugs from the same inhaler, or at least the same kind of inhaler that operates the same way.

Leach: In the early 1990s the Food and Drug Administration asked us for a dose-response study on QVAR. We decided that the only way to do it was to have patients come in 5 days a week for observation and training. And, as cited in the Busse et al study, we found a very significant dose-response relationship. Our assumption was that in past studies no one had forced patients to be that compliant. With some new drugs that are not quite as safe but are very effective, we have to find ways to make sure people are compliant in the clinical trials.

REFERENCE
and not reaching the lungs. I don’t know if that preference translated into the patients using their device more correctly or more often.

Rau: Apter and colleagues’ studied patients’ knowledge and beliefs about the effectiveness of the drug, and that certainly links to whether they think they are getting the medication or not. If they don’t think they are—and this has happened with the Proventil HFA inhaler, because of its softer, gentler aerosol plume—then patients worry that they’re not getting the medication. Who knows what that might lead to?

REFERENCE
