Determinants of Patient Adherence to an Aerosol Regimen

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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 β_2 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.

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] Bauman 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, 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."[5] In a 1995 publication, Tashkin defined compliance "simply as following the instructions of the health-care provider."[6] 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.[7] 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."[8] 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."[9] 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*.[9] 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.[10] 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).[11] 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.

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Table 1. General Types of Nonadherence to Prescribed Aerosol Therapy and Potential Factors That Can Predispose to Each Type*

Unintentional: Patient does not understand therapy correctly
Misunderstanding prescribed drug regimen (poor doctor-patient communication)[12]
Incorrect aerosol device technique
Language barriers
Intentional: Patient understands therapy but does not adhere correctly
Patient beliefs
I do not really require regular medication
I am not really sick
I gain attention from parents, am kept at home (children)
The medication is too expensive
I have concern about adverse effects
I do not perceive effect from the medication
Forgetfulness
Stress and busy lifestyle
Complex, demanding aerosol regimens
Psychological factors (eg, depression)[13]

*Two general categories of nonadherence are based on Reference 11.

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 Turbuhaler 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 β 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 β 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 β agonists and 32% for inhaled steroids. Only β_2 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.

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

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

*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

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,[25–27] as well as COPD.[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.[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. Jónasson 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.[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.[27] Such findings raise questions about the validity of clinical trials, when patient medication use is thought to be best.

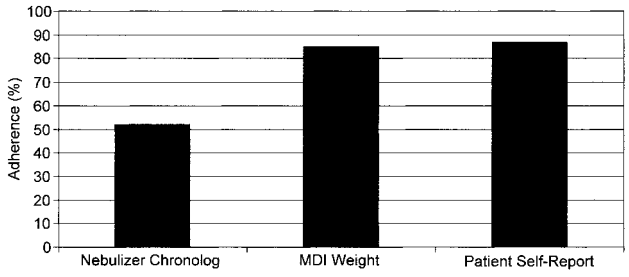

Fig. 1. Percentage of adherence with prescribed metered-dose inhaler (MDI) medication among patients with chronic obstructive pulmonary disease, determined with 3 methods of monitoring: nebulizer chronolog (electronic MDI monitor), MDI canister weight change, and patient self-report. (Based on data from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

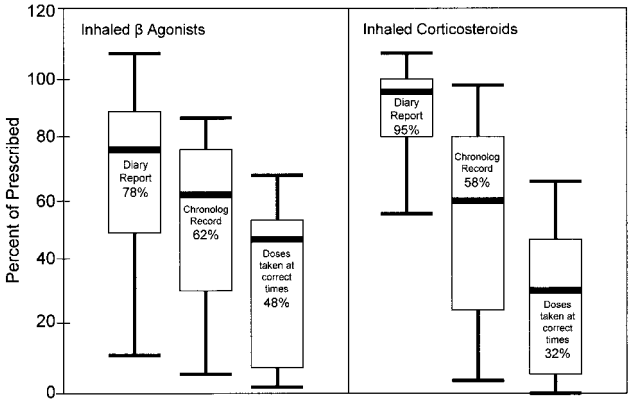

Fig. 2. Percentage of prescribed doses of inhaled β_2 agonists and inhaled corticosteroids over 13 weeks among asthmatic children. The chronolog record is the raw percentage of prescribed doses taken. "Doses taken at correct times" represents the percentage of prescribed doses with the correct number of puffs taken within the correct time window. The error bars indicate the minimum and maximum percentages. The boxes indicate the lower and upper quartiles (25% and 75% of subjects). The thick black horizontal bars indicate the medians of values reported or measured. (Adapted from Reference 4, with permission.)

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.

Table 3. Relation of Dosing Frequency to Compliance With a Prophylactic Inhaled Medication in Children Monitored With a Nebulizer Chronolog Monitor

Prescribed Frequency (doses/day)	Reported Compliance (% of days)	Monitored Compliance (% of days)
2	96	71
3	90	34
4	69	18

(Adapted from Reference 16.)

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 fluni-

solide twice a day, and group B taking 2 inhalations every 6 hours.[41] 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.

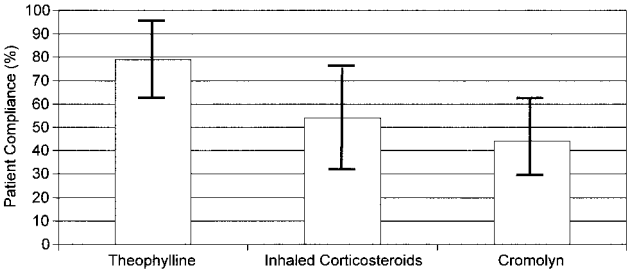

Fig. 3. Percentage of patient compliance with oral theophylline versus inhaled corticosteroids and cromolyn sodium, based on pharmacy claims data with a group of asthmatic subjects. The error bars represent the standard deviations. (Based on data from Reference 45.)

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 β_2 agonist (terbutaline) to a combination formulation of the two.[42] 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 β_2 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.[43] In addition, compliance was no better in patients using the combined formulation. These results may have been due to use of a short-acting β_2 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 β_2 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.[44] 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,[42] with a short-acting bronchodilator, and that of Stoloff et al,[44] 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.[44] 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.[45] 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

Table 4. Results on Adherence With Oral Versus Inhaled Medications From a Number of Studies

First Author, Year	Condition	Age Range (y)	Measurement	Adherence (%)	
				Oral Drug	Inhaled Drug
Kelloway 1994[45]	Asthma	12–65	Medical records Pharmacy data	Theophylline 79 ± 34	Corticosteroid 54 ± 43 Cromolyn 44 ± 34
Sherman 2001[46]	Asthma	Pediatric	Prescription refills	Montelukast 59 (95% CI 48–65)	Fluticasone 44 (95% CI 35–50)
Maspero 2001[47]	Asthma	6–11	Patient interview	Montelukast 82	Beclomethasone 45
Bukstein 2003[48]	Asthma	6–11	Patient self-report	Montelukast 78	Cromolyn 42
Jones 2003[49]	Asthma	6–55	Pharmacy claims	Leukotriene modifier 67.7	Inhaled corticosteroid 33.8 Long-acting β_2 agonist 40.0

CI = confidence interval

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 studies[46–49] 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.

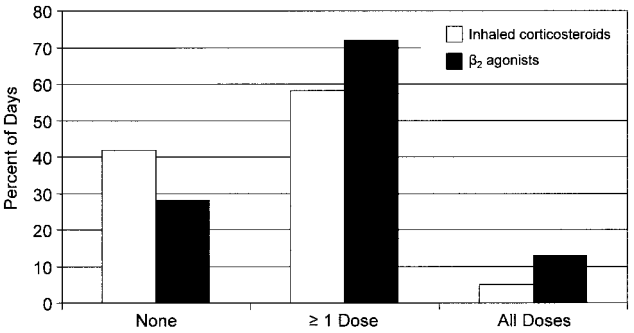

Fig. 4. Median percentage of days with no, minimal, or complete inhaled-medication use for corticosteroids and β_2 agonists among 24 asthmatic children. (Based on data from Reference 51.)

Type of Inhaled Medication: Inhaled Corticosteroids Versus β_2 Agonists

There is a perception among clinicians that patient adherence with prescribed inhaled corticosteroids is worse than with inhaled β_2 agonists. This has been attributed to the absence of immediate relief or perceptible effect from inhaled corticosteroids, compared to short-acting β_2 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 β_2 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 β_2 agonists. Milgrom et al measured adherence of children with asthma to regimens of both inhaled corticosteroids and β_2 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 β_2 agonists and 32% for inhaled corticosteroids. Median days without medication were 20.4% for β_2 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 β_2 agonists than with inhaled corticosteroids.[51] The results of their study are shown in Figure 4. The studies by Milgrom et al[4] and Bender et al[51] both support the view that inhaled corticosteroid adherence appears to be worse than adherence with inhaled β_2 agonists. It should be noted that in both studies the β_2 agonists were probably short-acting, as opposed to long-acting, although the specific drugs were not identified. Since inhaled corticosteroids and short-acting β_2 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 β_2 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

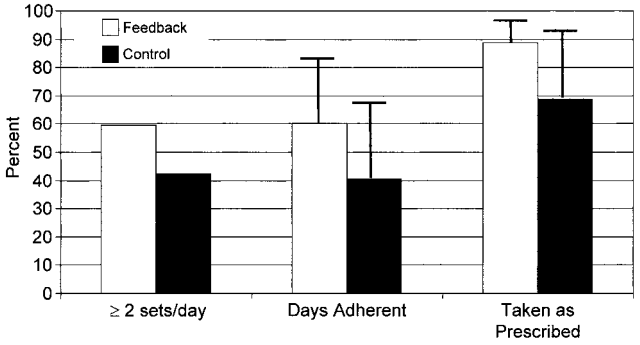

Fig. 5. Comparison of feedback and control groups on measures of adherence with metered-dose inhalers prescribed 3 times daily, among patients with chronic obstructive pulmonary disease. ≥ 2 sets/day = percentage who averaged ≥ 2 sets per day. Days Adherent = mean ± SD percent adherent days. Taken as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

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.[10] Nides et al divided COPD patients into a control group (n = 89) and a feedback group (n = 116).[52] 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 recorded the amount of inhaled drug used, whereas the feedback group was told of the device's ability to record the time and date of each MDI actuation. Adherence was recorded after a 4-month period. The mean ± SD number of MDI sets per day recorded by the nebulizer chronolog was 1.95 ± 0.68 for the feedback group and 1.63 ± 0.82 for the control group ($p = 0.003$). Figure 5 illustrates the percentage of patients who averaged 2 or more MDI sets per day, the mean percent of adherent days, and the mean percent of total MDI actuations taken as prescribed. Fifteen percent of the control group had "canister dumping" episodes, actuating their inhalers at least 100 times within a 3-hour period shortly before the 4-month follow-up visit. No canister dumping episodes occurred with subjects in the feedback group. Simmons et al also found that a feedback group exhibited better adherence than did a control group of COPD patients, over a 24-month follow-up period.[28] At 4 months the control group had 1.60 ± 0.83 sets of actuations per day, compared with 1.93 ± 0.69 in the feedback group (perfect compliance was 3.0 sets per day). For both groups, compliance fell over the 24 months of follow-up, with actuations per day of 1.16 ± 0.95 for the controls and 1.65 ± 0.89 for the feedback group at 24 months. Another study by Simmons et al found that 30 of 101 COPD subjects who were not informed of the function of the nebulizer chronolog actuated their inhalers > 100 times within a 3-hour interval on at least one occasion.[29] Only 1 of 135 subjects who had full knowledge of the nebulizer chronolog's recording ability did so. Dumping episodes usually occurred shortly before a clinic follow-up visit.

Patient Beliefs, Sociocultural, and Psychological Factors

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,[13] whereas 2 studies by Apter et al found the reverse.[53,54] Similarly, Horne and Weinman found that educational experience had no association with adherence,[56] but the studies by Apter et al found this was associated with adherence.[53–54] 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.[56] McQuaid et al found that older age had a negative association in a sample of children age 8–17 years.[57] 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.[25] A study by Labrecque et al reviewed pharmacy claims to investigate the effect of age on appropriate use of short-acting β_2 agonists among asthma patients.[58] 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.[59] 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

Table 5. Summary of Studies on the Effects of Health Beliefs; Demographics; Psychological, Sociocultural, and Socioeconomic Factors on Adherence With Aerosol Therapy

First Author, Year	Sample	Negative Association	No Association	Positive Association
Apter 1998[53]	Asthma Adults n=50 46±14yearsold (20–81yearsold)	< 12 years formal education Poor patient-clinician communication Income < $20,000 Spanish as first language Minority status	Asthma severity Locus of control measure Attitude toward inhaled corticosteroids	No variables found
Apter 2003[54]	Asthma Adults n = 85 47 ± 15 years old	African-American ethnicity Lower educational achievement Lower income More baseline symptoms	No variables found	Favorable attitude toward inhaled corticosteroids
Bender 1998[51]	Asthma Children n = 24 6–12 years old	Lower level of asthma knowledge Family dysfunction	Child behavior disorder	No variables found
Bosley 1995[13]	Asthma Adults n = 102 18–70 years old	Depression	Anxiety Interpersonal problems Gender Age Socioeconomic status	No variables found
Chambers 1999[55]	Asthma Adults n = 394 18–49 years old	Belief that inhaled corticosteroids were unnecessary if asymptomatic Concern over adverse effects	No variables found	Active participation in clinical decisions Asthma is a serious problem Recent hospitalization for asthma
Horne 1999[56]	Asthma (n = 78) others Adults n = 324 45.5 ± 18.3 years old	Concern over dependence Long-term effects	Gender Educational experience Number of prescribed medications	Higher necessity scores Asthma Older age
Labrecque 2003[58]	Asthma Adults and children n = 1,616 5–45 years old	Age group 15–45 years old (older age)	No variables found	No variables found
McQuaid 2003[57]	Asthma Children n = 106 8–16 years old	Older age Minority status Morbidity	Knowledge of asthma Responsibility for asthma Reasoning about asthma	No variables found

both asthma and COPD patients, the amount of rescue short-acting β_2 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 ± 38% in the run-in period to 92 ± 52% after education. However, compliance with an adjustment to the inhaled medications (specifically, doubling the inhaled steroid dose) was only 65 ± 30%. 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 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 β_2 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

(Compiled from References 11, 60, and 61.)

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,[14] 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.[7,11,60–61]

Lewis and Fink pointed out that the preparation of health-care professionals should emphasize the concept of partnership with patients to increase adherence.[62] 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.[62] 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.

REFERENCES

1. Birkhead G, Attaway NJ, Strunk RC, Townsend MC, Teutsch S. Investigation of a cluster of deaths of adolescents from asthma: evidence implicating inadequate treatment and poor patient adherence with medications. J Allergy Clin Immunol 1989;84(4):484–491.
2. Bauman LJ, Wright E, Leickly FE, Crain E, Kruszon-Moran D, Wade SL, Visness CM. Relationship of adherence to pediatric asthma morbidity among inner-city children. Pediatrics 2002;110(1):e6.
3. Williams LK, Pladevall M, Xi H, Peterson EL, Joseph C, Lafata JE, et al. Relationship between adherence to inhaled corticosteroids and poor outcomes among adults with asthma. J Allergy Clin Immunol 2004;114(6):1288–1293.
4. Milgrom H, Bender B, Ackerson L, Bowry P, Smith B, Rand C. Noncompliance and treatment failure in children with asthma. J Allergy Clin Immunol 1996;98(6):1051–1057.
5. Guralnik DB, editor. Webster's new world dictionary of the American language, 2nd College Ed. New York: Prentice Hall Press; 1984.
6. Tashkin DP. Multiple dose regimens: impact on compliance. Chest 1995;107(5):176S–182S.
7. Lewis RM, Fink JB. Promoting adherence to inhaled therapy: building partnerships through patient education. Respir Care Clin N Am 2001;7(2):277–301.
8. Mellins RB, Evans D, Zimmerman B, Clark NM. Patient compliance. Are we wasting our time and don't know it? (editorial) Am Rev Respir Dis 1992;146(6):1376–1377.
9. Rand CS, Wise RA. Measuring adherence to asthma medication regimens. Am J Respir Crit Care Med 1994;149(2):S69–S76.
10. Tashkin DP, Rand C, Nides M, Simmons M, Wise R, Coulson AH, et al. A nebulizer chronolog to monitor compliance with inhaler use. Am J Med 1991;91(Suppl 4A):33S–36S.
11. Cochrane GM, Horne R, Chanez P. Compliance in asthma. Respir Med 1999;93(11):763–769.
12. Farber HJ, Capra AM, Finkelstein JA, Lozano P, Quesenberry CP, Jensvold NG, et al. Misunderstanding of asthma controller medications: association with nonadherence. J Asthma 2003;40(1):17–25.
13. Bosley CM, Fosbury JA, Cochrane GM. The psychological factors associated with poor compliance with treatment in asthma. Eur Respir J 1995;8(6):899–904.
14. Mushlin AI, Appel FA. Diagnosing potential non-compliance: physician's ability in a behavioral dimension of medical care. Arch Intern Med 1977;137(3):318–321.
15. Rand CS, Wise RA, Nides M, Simmons MS, Bleecker ER, Kusek JW, et al. Metered-dose inhaler adherence in a clinical trial. Am Rev Respir Dis 1992;146(6):1559–1564.
16. Coutts JA, Gibson NA, Paton JY. Measuring compliance with inhaled medications in asthma. Arch Dis Child 1992;67(3):332–333.
17. O'Connor SL, Bender BG, Gavin-Devitt LA, Wamboldt MZ, Milgrom H, Szefler S, et al. Measuring adherence with the Doser CT in children with asthma. J Asthma 2004;41(6):663–670.
18. Bender B, Wamboldt FS, O'Connor SL, Rand C, Szefler S, Milgrom H, Wamboldt MZ. Measurement of children's asthma medication adherence by self report, mother report, canister weight, and Doser CT. Ann Allergy Asthma Immunol 2000;85(5):416–421.
19. Yeung M, O'Connor SA, Parry DT, Cochrane GM. Compliance with prescribed drug therapy in asthma. Respir Med 1994;88(1):31–35.
20. van der Palen J, Klein JJ, Rovers MM. Compliance with inhaled medication and self-treatment guidelines following a self-management programme in adult asthmatics. Eur Respir J 1997;10(3):652–657.
21. Bogen D, Apter AJ. Adherence logger for a dry powder inhaler: a new device for medical adherence research. J Allergy Clin Immunol 2004;114(4):863–868.
22. Krishnan JA, Riekert KA, McCoy JV, Stewart DY, Schmidt S, Chanmugam A, et al. Corticosteroid use after hospital discharge among

high-risk adults with asthma. Am J Respir Crit Care Med 2004; 170(12):1281–1285.
23. Jónasson G, Carlsen K-H, Sødal A, Jonasson C, Mowinckel P. Patient compliance in a clinical trial with inhaled budesonide in children with mild asthma. Eur Respir J 1999;14(1):150–154.
24. Burrows JA, Bunting JP, Masel PJ, Bell SC. Nebulised dornase alpha: adherence in adults with cystic fibrosis. J Cyst Fibrosis 2002; 1(4):255–259.
25. Jónasson G, Carlsen K-H, Mowinckel P. Asthma drug adherence in a long term clinical trial. Arch Dis Child 2000;83(4):330–333.
26. Cheng NG, Browne GJ, Lam LT, Yeoh R, Oomens M. Spacer compliance after discharge following a mild to moderate asthma attack. Arch Dis Child 2002;87(4):302–305.
27. Mawhinney H, Spector SL, Kinsman RA, Siegel SC, Rachelefsky GS, Katz RM, Rohr AS. Compliance in clinical trials of two nonbronchodilator, antiasthma medications. Ann Allergy 1991;66(4):294–299.
28. Simmons MS, Nides MA, Rand CS, Wise RA, Tashkin DP. Trends in compliance with bronchodilator inhaler use between follow-up visits in a clinical trial. Chest 1996;109(4):963–968.
29. Simmons MS, Nides MA, Rand CS, Wise RA, Tashkin DP. Unpredictability of deception in compliance with physician-prescribed bronchodilator inhaler use in a clinical trial. Chest 2000;118(2):290–295.
30. Orehek J, Gayard P, Grimaud C, Charpin J. Patient error in use of bronchodilator metered aerosols. Br Med J 1976;1(6001):76.
31. McFadden ER Jr. Improper patient techniques with metered dose inhalers: clinical consequences and solutions to misuse. J Allergy Clin Immunol 1995;96(2):278–283.
32. Guidry GG, Brown WD, Stogner SW, George RB. Incorrect use of metered dose inhalers by medical personnel. Chest 1992;101(1):31–33.
33. Jones JS, Holstege CP, Riekse R, White L, Bergquist T. Metered-dose inhalers. Do emergency health care providers know what to teach? Ann Emerg Med 1995;26(3):308–311.
34. Interiano B, Guntupalli KK. Metered-dose inhalers. Do health care providers know what to teach? Arch Intern Med 1993;153(1):81–85.
35. Lindgren S, Bake B, Larsson S. Clinical consequences of inadequate inhalation technique in asthma therapy. Eur J Respir Dis 1987;70(2): 93–98.
36. Hanania NA, Wittman R, Kesten S, Chapman KR. Medical personnel's knowledge of and ability to use inhaling devices: metered-dose inhalers, spacing chambers, and breath-actuated dry powder inhalers. Chest 1994;105(1):111–116.
37. Kesten S, Zive K, Chapman KR. Pharmacist knowledge and ability to use inhaled medication delivery systems. Chest 1993;104(6):1737–1742.
38. Melani AS, Zanchetta D, Barbato N, Sestini P, Cinti C, Canessa PA, et al. Inhalation technique and variables associated with misuse of conventional metered-dose inhalers and newer dry powder inhalers in experienced adults. Ann Allergy Asthma Immunol 2004;93(5): 439–446.
39. Eisen SA, Miller DK, Woodward RS, Spitznagel E, Przybeck TR. The effect of prescribed daily dose frequency on patient medication compliance. Arch Intern Med 1990;150(9):1881–1884.
40. Cramer JA, Mattson RH, Prevey ML, Scheyer RD, Ouellette VL. How often is medication taken as prescribed? A novel assessment technique. JAMA 1989;261(22):3273–3277.
41. Mann M, Eliasson O, Patel K, ZuWallack RL. A comparison of the effects of *bid* and *qid* dosing in compliance with inhaled flunisolide. Chest 1992;101(2):496–499.
42. Bosley CM, Parry DT, Cochrane GM. Patient compliance with inhaled medication: does combining β-agonists with corticosteroids improve compliance? Eur Respir J 1994;7(3):504–509.
43. Wasserfallen J-B, Baraniuk JN. Clinical use of inhaled corticosteroids in asthma. J Allergy Clin Immunol 1996;97(1 Pt 2):177–182.
44. Stoloff SW, Stempel DA, Meyer J, Stanford RH, Carranza Rosenzweig JR. Improved refill persistence with fluticasone propionate and salmeterol in a single inhaler compared with other controller therapies. J Allergy Clin Immunol 2004;113(2):245–251.
45. Kelloway JS, Wyatt RA, Adlis SA. Comparison of patients' compliance with prescribed oral and inhaled asthma medications. Arch Intern Med 1994;154(12):1349–1352.
46. Sherman J, Patel P, Hutson A, Chesrown S, Hendeles L. Adherence to oral montelukast and inhaled fluticasone in children with persistent asthma. Pharmacotherapy 2001;21(12):1464–1467.
47. Maspero JF, Duenas-Meza E, Volovitz B, Pinacho Daza C, Kosa L, Vrijens F, Leff JA. Oral montelukast versus inhaled beclomethasone in 6- to 11-year-old children with asthma: results of an open-label extension study evaluating long-term safety, satisfaction, and adherence with therapy. Curr Med Res Opin 2001;17(2):96–104.
48. Bukstein DA, Bratton DL, Firriolo KM, Estojak J, Bird SR, Hustad CM, Edelman JM. Evaluation of parental preference for the treatment of asthmatic children aged 6 to 11 years with oral montelukast or inhaled cromolyn: a randomized, open-label, crossover study. J Asthma 2003;40(5):475–485.
49. Jones C, Santanello NC, Boccuzzi SJ, Wogen J, Strub P, Nelsen LM. Adherence to prescribed treatment for asthma: evidence from pharmacy benefits data. J Asthma 2003;40(1):93–101.
50. Cochrane MG, Bala MV, Downs KE, Mauskopf J, Ben-Joseph RH. Inhaled corticosteroids for asthma therapy: patient compliance, devices, and inhalation technique. Chest 2000;117(2):542–550.
51. Bender B, Milgrom H, Rand C, Ackerson L. Psychological factors associated with medication nonadherence in asthmatic children. J Asthma 1998;35(4):347–353.
52. Nides MA, Tashkin DP, Simmons MS, Wise RA, Li VC, Rand CS. Improving inhaler adherence in a clinical trial through the use of the nebulizer chronolog. Chest 1993;104(2):501–507.
53. Apter A, Reisine S, Affleck G, Barrows E, ZuWallack RL. Adherence with twice-daily dosing of inhaled steroids: socioeconomic and health-belief differences. Am J Respir Crit Care Med 1998;157(6): 1810–1817.
54. Apter AJ, Boston RC, George M, Norfleet AL, Tenhave T, Coyne JC, et al. Modifiable barriers to adherence to inhaled steroids among adults with asthma: it's not just black and white. J Allergy Clin Immunol 2003;111(6):1219–1226.
55. Chambers CV, Markson L, Diamond JJ, Lasch L, Berger M. Health beliefs and compliance with inhaled corticosteroids by asthmatic patients in primary care practices. Respir Med 1999;93(2):88–94.
56. Horne R, Weinman J. Patients' beliefs about prescribed medicines and their role in adherence to treatment in chronic physical illness. J Psychosom Res 1999;47(6):555–567.
57. McQuaid EL, Kopel SJ, Klein RB, Fritz GK. Medication adherence in pediatric asthma: reasoning, responsibility, and behavior. J Pediatr Psychol 2003;28(5):323–333.
58. Labrecque M, Laurier C, Champagne F, Kennedy W, Pare M, Cartier A. Effect of age on the conformity rate to short-acting β-agonist use criteria in asthma. J Asthma 2003;40(7):829–835.
59. Gallefoss F, Bakke PS. How does patient education and self-management among asthmatics and patients with chronic obstructive pulmonary disease affect medication? Am J Respir Crit Care Med 1999;160(6):2000–2005.
60. Rubin BK. What does it mean when a patient says, "My asthma medication is not working"? Chest 2004;126(3):972–981.
61. Chapman KR, Walker L, Cluley S, Fabbri L. Improving patient compliance with asthma therapy. Respir Med 2000;94(1):2–9.
62. Lewis RM, Fink JB. Promoting adherence to inhaled therapy: building partnerships through patient education. Respir Care Clin N Am 2001;7(2):277–301.

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]

REFERENCE

1. Nikander K, Arheden L, Denyer J, Cobos N. Parents' adherence with nebulizer treatment of their children when using an adaptive aerosol delivery (AAD) system. J Aerosol Med 2003;16(3):273–281.

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

Rau: That is a very good comment. The data from Nides and colleagues[1] clearly showed better adherence among patients who knew they were being monitored and received feedback.

REFERENCE

1. Nides MA, Tashkin DP, Simmons MS, Wise RA, Li VC, Rand CS. Improving inhaler adherence in a clinical trial through the use of the nebulizer chronolog. Chest 1993;104(2):501–507.

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-

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lines,[1] and most of the others, that person should be on a short-acting β agonist for rescue, perhaps a long-acting β agonist for control, perhaps a long-acting anticholinergic for control, and perhaps an inhaled corticosteroid. With the current way of the world, with devices being married to drugs in a proprietary fashion, and not every company offering every drug or device, that means that this patient with severe COPD is going to have to be using, daily, a minimum of 3, and perhaps 4, different inhaler systems, all of which operate differently, with different instructions. We've seen, as yesterday in the presentation, some examples of how horrendously difficult that can be.

It seems to me that just continuing to work on patient adherence and education is not the whole story, and somehow in some future time it's got to be easier for patients to get the drugs they need to take, according to the best evidence we have, in a more simple way. I think that perhaps would mean fewer different kinds of inhalers. That would require a different system than what we have currently, with each drug being married proprietarily to a patented device that doesn't apply to the other drugs.

REFERENCE

1. Pauwels RA, Buist AS, Calverley PM, Jenkins CR, Hurd SS; GOLD Scientific Committee. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD) Workshop summary. Am J Respir Crit Care Med 2001; 163(5):1256–1276; Respir Care 2001; 46(8):798–825.

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,[1] 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

1. Busse WW, Brazinsky S, Jacobson K, Stricker W, Schmitt K, Vanden Burgt J, et al. Efficacy response of inhaled beclomethasone dipropionate in asthma is proportional to dose and is improved by formulation with a new propellant. J Allergy Clin Immunol 1999;104(6):1215–1222.

Smaldone: I was amazed that the study by Rand et al[1] showed that patient diaries were not as accurate as the counters. Patients often bring me their diaries, particularly when they take oral prednisone, and tell me I took it here, I took it there. There's no reason, a priori, for me to believe or to disbelieve them. Maybe it's because they are bringing me their data rather than me saying to keep a diary. In that study did they ask patients to keep a diary? Maybe it was onerous for some patients and they faked it. I'm curious what they said about why diaries were so unreliable?

REFERENCE

1. Rand CS, Wise RA, Nides M, Simmons MS, Bleecker ER, Kusek JW, et al. Metered-dose inhaler adherence in a clinical trial. Am Rev Respir Dis 1992;146(6): 1559–1564.

Rau: They did speculate on that. They speculated that—and I think this is a big factor—patients want to please their physicians, so if they didn't take their 4 puffs or whatever they're still going to put a few hatch marks in the diary, because that's what you asked them to do. But it can also go the other way. The other reason may be they don't like you at all; you've got lousy patient/physician communication, so they're just going to lie to you. They say, "I don't care what he thinks, I will just say I used it and then I will do it the way I want to and see what happens." Those were the speculations. I don't think anybody knows.

Laube: There was a survey, conducted by Chapman, that examined patients' preferences for the Diskus versus the Turbuhaler.[1] Patients reported they preferred the Diskus over the Turbuhaler, because with the Diskus they could taste the drug and therefore felt that they were getting their treatment. With Turbuhaler they didn't taste the drug and therefore didn't feel like they were actually being treated. Of course, the fact that they were tasting it meant that a lot was depositing in the mouth

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

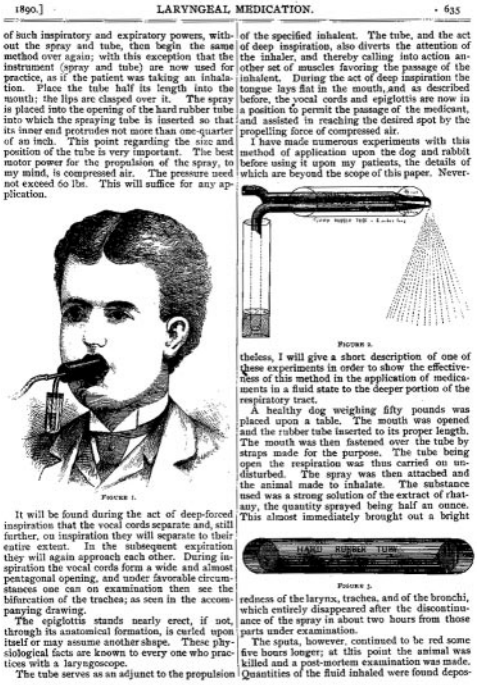
REFERENCE

1. Chapman KR. Effect of inhaled route of administration on compliance in asthma. Eur Respir Rev 1998;8:275–279.

Rau: Apter and colleagues[1] 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

1. Apter AJ, Reisine ST, Affleck G, Barrows E, ZuWallack RL. Adherence with twice-daily dosing of inhaled steroids: socioeconomic and health-belief differences. Am J Respir Crit Care Med 1998;157(6 Pt 1): 1810–1917.



1890.] LARYNGEAL MEDICATION. 635

of such inspiratory and expiratory powers, without the spray and tube, then begin the same method over again; with this exception that the instrument (spray and tube) are now used for practice, as if the patient was taking an inhalation. Place the tube half its length into the mouth; the lips are clasped over it. The spray is placed into the opening of the hard rubber tube into which the spraying tube is inserted so that its inner end protrudes not more than one-quarter of an inch. This point regarding the size and position of the tube is very important. The best motor power for the propulsion of the spray, to my mind, is compressed air. The pressure need not exceed 60 lbs. This will suffice for any application.

FIGURE 1.

It will be found during the act of deep-forced inspiration that the vocal cords separate and, still further, on inspiration they will separate to their entire extent. In the subsequent expiration they will again approach each other. During inspiration the vocal cords form a wide and almost pentagonal opening, and under favorable circumstances one can on examination then see the bifurcation of the trachea; as seen in the accompanying drawing.

The epiglottis stands nearly erect, if not, through its anatomical formation, is curled upon itself or may assume another shape. These physiological facts are known to every one who practices with a laryngoscope.

The tube serves as an adjunct to the propulsion of the specified inhalent. The tube, and the act of deep inspiration, also diverts the attention of the inhaler, and thereby calling into action another set of muscles favoring the passage of the inhalent. During the act of deep inspiration the tongue lays flat in the mouth, and as described before, the vocal cords and epiglottis are now in a position to permit the passage of the medicant, and assisted in reaching the desired spot by the propelling force of compressed air.

I have made numerous experiments with this method of application upon the dog and rabbit before using it upon my patients, the details of which are beyond the scope of this paper. Nevertheless, I will give a short description of one of these experiments in order to show the effectiveness of this method in the application of medicaments in a fluid state to the deeper portion of the respiratory tract.

FIGURE 2.

A healthy dog weighing fifty pounds was placed upon a table. The mouth was opened and the rubber tube inserted to its proper length. The mouth was then fastened over the tube by straps made for the purpose. The tube being open the respiration was thus carried on undisturbed. The spray was then attached and the animal made to inhalate. The substance used was a strong solution of the extract of rhatany, the quantity sprayed being half an ounce. This almost immediately brought out a bright

FIGURE 3.

redness of the larynx, trachea, and of the bronchi, which entirely disappeared after the discontinuance of the spray in about two hours from those parts under examination.

The sputa, however, continued to be red some five hours longer; at this point the animal was killed and a post-mortem examination was made. Quantities of the fluid inhaled were found depos-

Bleyer's bronchial spray, 1890
Article from *JAMA* 1890 by J Mount Bleyer MD,
explaining a novel method for using a spray to administer
medications to the deeper portions of the respiratory tract
Courtesy Mark Sanders, Inhalatorium, http://inhalatorium.com/