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. © 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] 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.

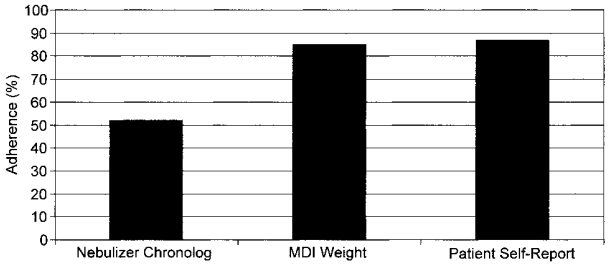

Fig. 1. Percentage of adherence with prescribed metered-dose inhaler (MDI) medication among patients with chronic obstructive pulmonary disease, determined with 3 methods of monitoring: nebulizer chronolog (electronic MDI monitor), MDI canister weight change, and patient self-report. (Based on data from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

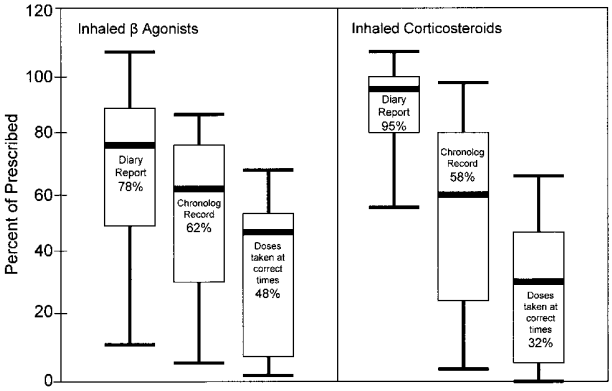

Fig. 2. Percentage of prescribed doses of inhaled β_2 agonists and inhaled corticosteroids over 13 weeks among asthmatic children. The chronolog record is the raw percentage of prescribed doses taken. "Doses taken at correct times" represents the percentage of prescribed doses with the correct number 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-

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