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# Should patients with persistent severe asthma be monitored for medication adherence?

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**Background:** Poor asthma outcomes often result from patients not following physician medication recommendations (ie, nonadherence). Estimates suggest that 50% of patients with asthma do not follow physician medication recommendations.

**Objective:** To examine the rationale for making available objective medication adherence monitors for physicians to improve the quality of care for patients with severe persistent asthma.

**Methods:** Review of the literature was undertaken in the following areas related to asthma: cost, morbidity, adherence, adherence monitoring, outcomes, and guidelines.

**Results:** Patients with severe asthma are at risk for nonadherence because of (1) the use of multiple medications to control symptoms, (2) coexisting disease states, (3) the occurrence of depression and anxiety, and (4) the high cost of care. Research studies have demonstrated the effectiveness of objective monitoring as part of multiple clinical strategies to improve adherence and reduce morbidity and the cost of asthma care. Without objective adherence monitoring, physicians may not accurately assess nonadherence as the cause of treatment failure. This may lead to inappropriate increases in therapy, diagnostic studies, and consultations and may leave the patient at risk for persistent symptoms, morbidity, and death.

**Conclusion:** By correctly assessing nonadherence as the cause of treatment failure in patients with not only severe asthma but mild and moderate disease as well, practicing physicians may improve the quality of care provided.

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## INTRODUCTION

Asthma is the fourth most prevalent chronic disease in the United States, and it has a significant impact on individuals with the disease and on those who pay for the care. Asthma is the most prevalent disease of childhood and young adulthood.<sup>1</sup> In 2001, it was estimated that 20.1 million individuals had the diagnosis of asthma.<sup>1</sup> Asthma results in considerable morbidity and even in mortality. In 2000, there were 1.8 million emergency department visits, 465,000 hospitalizations, and 4,487 deaths as a result of asthma.<sup>1</sup>

## COSTS OF ASTHMA CARE

The annual cost of asthma in 1998 was estimated to be \$12.7 billion.<sup>2</sup> Thirty-two percent of the direct costs were related to hospital (inpatient and emergency) care. Two studies<sup>3,4</sup> in the United States found that cost increases were proportional to the severity of disease. Annual mean costs for mild, moderate, and severe asthma were \$2,316, \$4,088, and \$11,066, respectively.<sup>4</sup> A similar relationship between severity of asthma and cost of care has been observed in Canada and Australia.<sup>5,6</sup> The accuracy of the previous severity classification data may be limited given the poor agreement among asthma specialists evaluating the severity of disease in similar patients.<sup>7</sup> The relationship between cost of asthma care and adherence to anti-inflammatory medication therapy has been indirectly studied by Suissa et al,<sup>8</sup> who correlated adult hos-

pitalization with pharmacy refill rates for inhaled corticosteroids. A direct relationship between patient anti-inflammatory medication use and cost has not been reported because there are no adherence assays for leukotriene modifiers or effective adherence devices for metered-dose inhalers (MDIs) (pressure or dry powder) in clinical practice.

## ADHERENCE

Medication adherence can be defined as the degree to which patient medication use corresponds with the prescribed regimen.<sup>9</sup> It is estimated that less than 50% of patients with asthma follow preventive anti-inflammatory therapy recommendations.<sup>10</sup> Estimates are derived from research and clinical studies that use varying subjective measures (patient diary) and objective measures (electronic medication monitors, prescription refill data, and weight of MDI). Researchers have quantified adherence to inhaled corticosteroid therapy by using MDIs equipped with microprocessor technology.

Using these research electronic devices, various studies found that adherence for adult patients was 37%<sup>11</sup> and 47%,<sup>12</sup> and pediatric patients had adherence rates of 45%<sup>13</sup> and 50%.<sup>14</sup> Using prescription refill data from a large managed care organization, investigators studied the number of prescription refills for anti-inflammatory medications by members 12 years and older during 1 year.<sup>15</sup> They found that the refill rate for the fluticasone pressure MDI was 2.27; rates for the fluticasone-salmeterol dry powder MDI and montelukast were 4.06 and 4.51, respectively.

It is a common misconception to think that patients with severe disease are more conscientious and follow a treatment plan to avoid symptoms. Two studies, using electronic mon-

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itors, document poor adherence by patients with severe asthma. In a study of pediatric patients with asthma, Milgrom et al<sup>16</sup> demonstrated that prednisone bursts were more common in patients who were found by electronic monitoring to be the least adherent to inhaled anti-inflammatory therapy. Similarly, Mann et al<sup>17</sup> found that adherence during a 9-week period to inhaled corticosteroid therapy by adults with moderate-to-severe asthma decreased during times of decreased pulmonary function.

### **PATIENTS OVERSTATE ADHERENCE**

An increasing knowledge base documents that many patients with anti-inflammatory MDIs do not accurately report adherence to their physicians. This finding has been demonstrated in adult and pediatric patients by using microchip technology.<sup>11–13,16,18</sup> Milgrom et al<sup>16</sup> evaluated adherence in 24 children with moderate-to-severe asthma who were prescribed an inhaled corticosteroid and who were monitored electronically without their knowledge. Diary card data showed that patients reported taking all doses on a median of 54% of study days and at least 1 dose on a median of 97% of study days. However, electronic records of inhaled corticosteroid use showed that these values were actually 5% and 58%, respectively. Misrepresentation of medication use also occurs in clinical practice.<sup>19</sup>

### **TYPES OF NONADHERENCE**

Patients may be nonadherent with medication therapy for a variety of reasons. Rand<sup>20</sup> provided a framework for the functional classification of nonadherent behavior into 3 broad categories: erratic, unwitting, and intelligent. Erratic nonadherence is the most common. It refers to missed doses because of forgetfulness, schedule changes, or busy schedules. Unwitting nonadherence refers to patients who are inadvertently nonadherent with the prescribed therapy because they did not understand fully either the specifics of the regimen or the necessity for compliance. Intelligent nonadherence refers to patients who purposefully alter, discontinue, or even fail to initiate prescribed therapy. Patients alter prescribed therapy for a variety of reasons: they may feel physically improved and do not perceive the need to continue medication use; they may have concerns about adverse effects, taste, cost, or unfavorable lifestyle changes associated with treatment; or they may, through experimentation, determine a dosing schedule that is as effective as that prescribed by the physician.<sup>20</sup> Many patients are reluctant to inform their providers that they did not follow medical instructions. Because no objective adherence measures are available for practicing physicians, clinicians must rely on the “honor system,” which often leads to inaccurate diagnostic and therapeutic decisions.<sup>21</sup> Without objective adherence measures, physicians must rely on a more detailed medication history to evaluate adherence. Short-term studies have documented that open-ended communication, careful interviewing, and active listening can improve medication use.<sup>22</sup> However, many physi-

cians do not believe that they can spend adequate time with the patient to accurately gauge adherence to treatment.

### **PATIENTS WITH SEVERE ASTHMA ARE AT HIGH RISK FOR NONADHERENCE**

Patients with severe asthma may be at greater risk for non-adherence than those with less severe asthma for 4 reasons. First, they require more asthma medication (many by the inhaled route) to control severe symptoms.<sup>23–25</sup> Second, co-existing conditions that may aggravate or complicate asthma (such as gastroesophageal reflux; rhinosinusitis and polyps; sensitivity to aspirin, nonsteroidal anti-inflammatory drugs, and preservatives; and laryngeal dysfunction) require additional medical and pharmacologic treatments to reduce oral corticosteroid use.<sup>26</sup> Multiple studies have shown that medication adherence decreases as the number of medications prescribed, the dosing frequency, and the duration of treatment increase.<sup>27</sup> Adherence in children with mild asthma receiving budesonide by MDI in a long-term clinical trial<sup>28</sup> decreased from 76.9% at 3 months to 54.2% at 9 months and 48.8% at 27 months. Third, patients with severe asthma have higher rates of depression and anxiety, which may contribute to poor adherence.<sup>29</sup> The incidences of depression and anxiety are increased in children and adolescents with severe asthma relative to comparison groups with mild asthma or no medical illness.<sup>30</sup> Psychiatric symptoms, particularly depression and anxiety, in children and their parents have been shown to be risk factors for increased nonadherence, morbidity, and mortality in patients with asthma.<sup>31–34</sup> Depression is also a risk factor for nonadherence in patients without chronic disease.<sup>35</sup> Fourth, persons with severe asthma must cope with the immediate and long-term impact of the illness, which affects their daily functioning, employability, and ability to pay for health care and medication. A study<sup>36</sup> of adult corticosteroid-dependent patients with asthma in the United States reported that patients had a median of \$1,926 in out-of-pocket expenses, which was 34% of the annualized per capita direct costs of \$8,156. Daily symptoms may reduce productivity while patients are at work and may limit long-term career opportunities.

### **MEDICATION MONITORING IMPROVES ADHERENCE**

Several asthma studies have documented that monitoring patients with asthma for adherence and giving feedback regarding medication use can improve patient adherence without any other intervention. Yeung et al<sup>37</sup> and Onyirimba et al<sup>38</sup> observed increased adherence to inhaled corticosteroid therapy in adults by giving feedback on medication use. Nides et al<sup>39</sup> similarly improved adherence to ipratropium bromide therapy by providing feedback to adult patients. Eney and Goldstein<sup>40</sup> improved adherence to theophylline therapy by reviewing blood levels with the parents of children with asthma.

A study<sup>41</sup> of adults with diabetes mellitus receiving oral medication contained in an electronic medication monitoring

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device documented the advantages of using this device compared with using a manual pill count. Investigators using the electronic medication monitoring device identified medication use patterns (inappropriate administration times, drug holidays, and use before clinic visits) and provided educational interventions appropriate to the cause of nonadherence. The objective adherence data prevented unwarranted pharmacologic manipulations based on an inaccurate medication history.

### **MONITORING WITH OTHER INTERVENTIONS**

The short-term adherence monitoring studies<sup>37-41</sup> reviewed previously herein suggest that as a single strategy, feedback from medication monitoring can be effective in promoting adherence in a clinical setting. However, none of these asthma adherence monitoring studies were conducted in an extended randomized clinical trial, and, therefore, their actual effectiveness is not known. Although adherence monitoring with feedback, by itself, might be an effective strategy for some patients, it could be anticipated that other individuals may not change their medication use patterns with this single intervention. Other interventions—organizational, behavioral, motivational, and educational—most likely will be required to improve adherence.

Two reviews<sup>42,43</sup> of randomized controlled adherence interventions in chronic diseases, including asthma, suggest that current methods of improving adherence for chronic health problems (more convenient care, information, counseling, reminders, self-monitoring, reinforcement, family therapy, and increased supervision) are mostly complex, labor intensive, and not predictably effective. Bender et al<sup>43</sup> evaluated 16 randomized asthma adherence intervention studies (educational or behavioral). Seven studies demonstrated no improvement in adherence. Of the 9 studies that reported improvements in adherence and symptom control, most relied on patient reports of adherence, raising questions about the validity of the study findings. The authors encouraged the use of innovative interventions with objective adherence measures to validate the study design.

### **INNOVATIVE STUDIES: PROMOTING ADHERENCE AND REDUCING COST**

Two innovative, nonrandomized studies that used objective monitoring with multiple interventions to promote adherence give promise for further controlled investigation. Bartlett et al<sup>44</sup> initiated a pilot project with 15 inner-city asthmatic children, aged 7 to 12 years, to evaluate the effectiveness of combining adherence electronic monitoring of inhaled corticosteroid asthma therapy and social learning strategies. These behavioral strategies, delivered by home-visiting nurses, included goal setting, monitoring, feedback reinforcement, behavioral contracting, and enhanced self-efficacy. The electronic medication adherence monitor provided adherence information to the parents of the children. At baseline, only 28.6% of the children were using their medications as prescribed. At the end of the 4-week intervention, the proportion

of children using medications as prescribed increased to 54.1%.

One group of investigators combined medication monitoring with a psychoeducational self-management program for children with severe asthma and their families in an inpatient rehabilitation setting.<sup>45,46</sup> This rehabilitation intervention included medical evaluation and management, physical exercise training, asthma education for the child and family, and a sequence of family interviews designed to facilitate home management of the illness and promote medication adherence. These individuals were receiving 3 to 4 medications daily, with most receiving theophylline. They were monitored by theophylline levels at each outpatient visit after discharge from inpatient rehabilitation. The year before entry into the inpatient rehabilitation program, the 59 children with severe asthma had a median of 7 hospital days and 4 emergency department visits. The median number of hospital days and emergency department visits at all 4 years of outpatient follow-up was zero. Median cost during the year before rehabilitation was \$10,240. Median cost at the first-year follow-up was \$4,036; second year, \$2,801; third year, \$2,316; and fourth year, \$1,936.<sup>47</sup> It is difficult to determine the cause(s) of the outcomes from both studies because of the multiple interventions provided. Both were labor intensive and costly. Future research in a controlled setting with fewer interventions may evaluate the cost-effectiveness of electronic monitoring devices and assays for leukotriene modifiers.

### **COST AND ACCURACY OF MONITORING**

#### *Electronic Monitors*

Monitoring costs vary depending on the technology used. Assays for leukotriene modifiers currently exist in pharmaceutical companies' laboratories and can be released to clinical laboratories for physician use. These tests, performed by high-pressure liquid chromatography, would be priced for payers at costs (\$50-\$75) similar to those of other tests currently performed by this method. Electronic monitors vary in cost, depending on the technology used, and are available only for pressure MDIs.

Although manufacturers of MDIs are providing counting devices for patients on these new products, these have limited use as monitors because they do not record the date and time of use. Two monitoring devices are available for purchase. The Doser CT (Meditrack Products, Hudson, MA) is placed on the top of the canister and records the date and time of actuation during a 40-day period. It has a small screen to view the results. It does not give a record of inspiration, an important feature to document use, and there is no written record of adherence. The cost is approximately \$30, and the device can be reused on other MDIs. The MDILog II (Medtrac Technologies, Englewood, CO) is placed on the plastic sleeve of the MDI and records the date and time of actuation and shaking and the quality of inspiration. It can store 1,300 actuations and can be reused on other MDIs. The data are

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transferred through an infrared port to a personal computer, allowing for a written record that can be reviewed with the patient and potential third-party billing. It has a modem option that can transfer data from the patient's home. The cost of the software and port is approximately \$1,000. The MDILogII is approximately \$300. A study<sup>48</sup> on an earlier generation of this device found errors in reporting use. Three studies<sup>49-51</sup> of a newer model were more favorable regarding accuracy in recording the sequencing of shaking, dispensing, and inhaling. However in one study,<sup>50</sup> periodic malfunctioning of a single MDILog II was responsible for decreasing the accuracy data of the group of 6 units being studied.

Compared together in one study,<sup>51</sup> there was no statistical difference in the accuracy of the Doser CT (94.3%) vs the MDILogII (90.1%), with the authors noting that both devices are sufficiently accurate to monitor adherence in most clinical settings. Although the cost of the available technology is considerable, there may be significant value for payers, providers, and patients with persistent asthma to determine whether nonadherence is the cause of treatment failure. Health systems may be more likely to use costly technology for patients who have been hospitalized for asthma. They would do so in anticipation that nonadherent behavior could be recognized and modified to reduce symptoms and costs related to persistent asthma, reduced quality of life, and disability. As the demand for monitoring increases, production costs should fall, making adherence monitoring more cost-effective and more available for patients with mild and moderate persistent disease.

#### *Pharmaceutical Monitors and Interventions*

Records of medication refills can provide physicians with objective information on medication adherence. A study comparing physicians' perceptions of patient adherence with actual pharmacy patient records demonstrated that providers underestimated patient adherence and that pharmacy records were an accurate and practical method of identifying adherence.<sup>19</sup>

Pharmacy records have been used to measure adherence to inhaled corticosteroid therapy in large asthmatic populations<sup>8</sup> and to evaluate the effectiveness of practitioners following asthma treatment guidelines.<sup>52</sup> Pharmaceutical interventions that include refill reminders combined with unit-of-use packaging have been shown to enhance adherence to second-generation sulfonylurea glyburide therapy twice daily and to decrease physician, laboratory, and hospital services compared with routine pharmacy care.<sup>53</sup> Two issues currently limit the use of refill data in promoting adherence. The first is the current lack of availability of this service for many patients. The increased use of computerized medical records in the future will allow point-of-service intervention in either the physician's office or the pharmacy. The second is the incorrect classification of many patients with asthma.<sup>7</sup> For example, a symptomatic patient thought to have persistent asthma who actually has intermittent asthma would be incorrectly diagnosed as being nonadherent based on refill data.

Direct electronic monitoring would help clarify the adherence of this patient by giving the monitoring device and MDI when he or she is symptomatic.

#### **IMPROVE THE QUALITY CONTROL OF ASTHMA CARE**

The absence of adherence measures in health care contributes to costly asthma outcomes and poor quality control. Quality control of product production or services rendered depends on the ability to evaluate the quality of each component of the process.<sup>54</sup> This is essential for products or services that may result in the user's or recipient's injury or death. For this reason, the US government regulates "high-risk" industries such as those related to automobiles and health care. For example, the federal government regulates the production and function of critical components of automotive vehicles. State governments issue licenses to operators who demonstrate comprehension of driving regulations. States enforce laws that promote motor vehicle safety. At the time of injury or death due to a motor vehicle accident, an investigation determines the cause. Government regulations and laws exist to objectively determine the responsibility of the driver (alcohol and drug use) and manufacturer (production defects). Likewise, the government regulates the health care industry's production of all prescribed therapeutics and medical equipment, and it licenses providers. However, no objective tests are available to determine the cause of hospitalization and death caused by patient nonadherence to treatment recommendations.<sup>55</sup> This is notably the case for asthma care, in which physicians cannot monitor for adherence patients who receive anti-inflammatory medications (leukotriene antagonists and inhaled corticosteroids), which are recommended by the Global Initiative for Asthma guidelines for daily preventive therapy.<sup>56</sup> Many symptomatic patients who are misdiagnosed as being adherent receive inappropriate, expensive, and inefficient care. If physicians could objectively determine adherence status, they could correctly manage ineffective treatment, offer targeted programs to promote adherence, and possibly prevent future unnecessary hospitalizations and death from asthma.

Current treatment guidelines are appropriate for adherent patients with symptomatic asthma only (Fig 1). To make the guidelines appropriate for adherent and nonadherent patients with symptomatic asthma, physicians must have the necessary diagnostic adherence monitors for clinical use (Fig 2). By objectively evaluating the adherence of symptomatic patients, those who are not adherent may be identified, appropriately treated, and counseled in an accurate, efficient, and cost-effective manner.<sup>57</sup>

#### **SUPPORTING THE DEVELOPMENT OF ADHERENCE MONITORING**

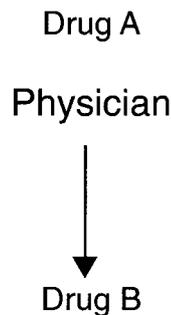
A recent report by the World Health Organization underscores the need for an integrated approach to improve patient adherence. The authors stress that providers of care must work in systems that support their capability to effectively

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**Current Guidelines  
Adherent Asthmatics**

Symptomatic Patient



**Consider Specialty Referral**

Figure 1. Current asthma guidelines presume that all symptomatic patients who have a history of medication adherence should receive further treatment or evaluation to reduce symptoms. These guidelines are not functional for nonadherent patients who are mistakenly thought to be adherent and therefore receive unnecessary and inappropriate care.

promote adherence. This includes training in adherence management, technology to diagnose adherence status, and reimbursement for services provided, with appropriate billing codes.<sup>58</sup> *Current Procedural Terminology* code 94014 has been established for billing patient-initiated remote spirometric recording per 30-day period.<sup>59</sup> The billing for this important physiologic measure of asthma care includes reinforced education, transmission of spirometric tracing, data capture, analysis of transmitted data, periodic recalibration, and physician review and interpretation. Development of *Current Procedural Terminology* codes for remotely collected electronic, objective adherence monitoring will promote the use of this important aspect of clinical practice and assist in essential patient management decisions. Pharmacy refill data that give physicians important information about their patients' clinical course for an extended period are not routinely available, but they should be. Improved communication (telephone and electronic) between physicians and pharmacists would add to the objective data that lead to an accurate evaluation of adherence status.

**ETHICAL ISSUES IN ADHERENCE PROMOTION AND MONITORING**

Rand and Sevick<sup>60</sup> and Hess<sup>61</sup> discussed ethical issues that practitioners and researchers must consider when intervening to increase adherence to medical treatments, including respecting the patient's best interests, autonomy, and privacy. With the advent of microprocessor monitoring technology for adherence in most disease states, there should be a careful

**Possible Future Guidelines  
Adherent & Non-Adherent Asthmatics**

Symptomatic Patient

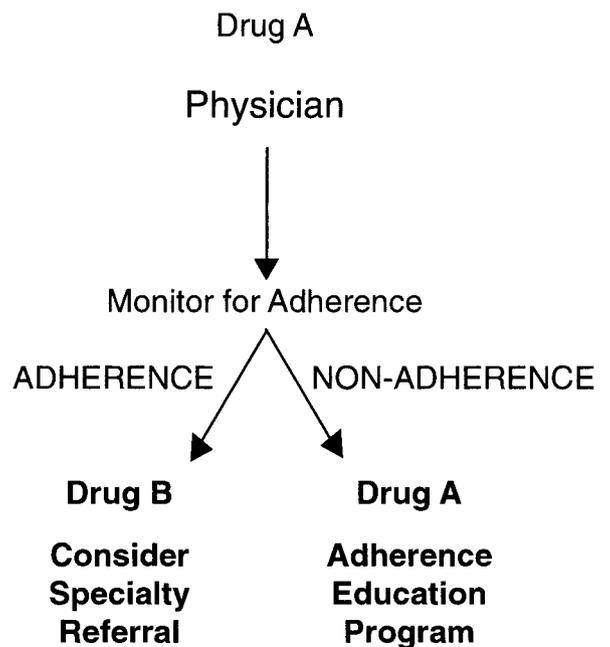


Figure 2. Objective adherence monitoring allows the clinician to accurately determine the adherence status of symptomatic patients and thus to improve the efficiency and quality of care. These modified asthma guidelines permit increasing the level of care for symptomatic adherent patients and providing adherence educational programs for patients who are identified as nonadherent.

examination of the ethical implications of this practice in clinical medicine in relation not only to the patient but also to employers and third-party payers. Objective adherence data may document that a patient's suboptimal adherence may have led to increased morbidity and subsequent health care costs. These data could be used by a payer to make determinations about the future risk or costs of providing health care to an individual or about denying insurance coverage altogether.<sup>60</sup> Physicians will need to consider how monitoring and recording adherence will affect the overall best interest of the patient. Specific guidelines for clinical adherence monitoring would be helpful for practitioners using this technology. Although researchers may use adherence monitoring in specific situations without informing the patient, covert or unacknowledged monitoring violates the patient's right to privacy and the principle of autonomy. Seeking the permission of the patient for adherence monitoring makes good clinical sense in that it promotes physician-patient communication and partnership in care.

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## CONCLUSION

The reasons to monitor patients with severe persistent asthma include the following: (1) prevention of morbidity and mortality, (2) reduction in costs for unnecessary emergency and inpatient services, and (3) improvement in quality controls for health care. These arguments are also valid for monitoring patients with less severe disease, who are prescribed daily controller medication. Presumably, identifying nonadherent behavior in patients with less severe disease will reduce the probability of developing severe symptoms. Controlled clinical trials are required to test the effectiveness of medication monitoring by itself and in conjunction with varying clinical management strategies (educational and behavioral) in improving patient adherence. Physicians who care for the most critically ill patients with asthma need to have diagnostic tools that objectively measure the medication adherence status of symptomatic patients with asthma. The question that will be addressed in the near future is not whether patients with severe asthma should be objectively monitored for adherence but rather which patients need to be monitored and by what diagnostic method and which clinical strategy will yield the best improvements in the adherence of each individual.

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