Chapter 7
Impact of Medication Delivery Method on Patient Adherence

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Synopsis

In this chapter, we provide a systematic review of randomized controlled trials, meta-analysis, case-control, or cohort studies that compared patient adherence with, or preference for, oral or inhaled controller medication for asthma. Among 17 studies meeting inclusion criteria for our review, patients were more adherent to oral than inhaled medications. Where queried, patients or parents expressed preference for oral medications. These findings were consistent across study designs, using contrasting measures of adherence, over varied time periods and including many with 12-month follow-up, and with patients who knew they were being monitored as well as those included in an anonymous database. Indirect evidence indicates that patient's preference for oral medication is not related to dosing frequency.

Introduction

Many patients with asthma are not adherent with treatment. Despite more than a decade of evidence-based physician guidelines for the management of asthma, hospitalization and emergency department visits for asthma remain high. Large, multinational, community-based surveys of asthma have shown that the majority of asthma patients suffer from alarmingly high rates of symptoms and disruption of life from their disease (Adams et al. 2002; Lai et al. 2003; Rabe et al. 2004). The tools to control asthma and prevent hospitalization are in place. Daily controller medicine can effectively treat most asthma symptoms, reducing airway inflammation and health care utilization (Szefler et al. 2000; Masoli et al. 2004; Schatz et al. 2003; Bateman et al. 2004). However, even the most effective medications have little value if not taken as prescribed.

Adherence to inhaled corticosteroids (ICS) in real-world settings is poor in all patient groups and across countries (Cerveri et al. 1999; DiMatteo et al. 2002; Melnikow and Kiefe 1994). Estimates of adherence rates to therapeutic recommendations in long-term medical regimens range from 40 to 65% (Adherence to long-term therapies: Evidence for action 2003). Children with asthma frequently receive less than half of their prescribed ICS treatments (Walders et al. 2005; McQuaid et al. 2003; Gibson et al. 1995; Coutts et al. 1992; Creer and Bender 1993). Similar findings have been reported for adult patients (Beardon 1993; Barr et al. 2002; Rand and Wise 1996).

Poor adherence leads to poor asthma control. A recent study demonstrated that in a cohort of 405 adults with asthma from a large health maintenance organization, overall adherence to ICS was approximately 50%. Lower adherence to ICS was associated with increasing numbers of oral steroid fills, emergency department visits, and asthma-related hospitalizations (Williams et al. 2004). Patients with a visit to the emergency department for exacerbation of asthma increased their medication adherence only temporarily before quickly returning to baseline rates (Stempel et al. 2004). Similarly, less than half of corticosteroid prescriptions were filled after children were hospitalized for asthma (Cooper and Hickson 2001). Under-utilization of ICS has been repeatedly linked to poor asthma control, reflected in increased symptoms, hospitalization, and asthma-related death (Suissa et al. 2000; Donahue et al. 1997; Williams et al. 2004).

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Multiple, complex factors influence patient adherence. Understanding of the illness, socioeconomic status, race, lifestyle, physician behavior, symptoms, medication cost, patient mental health, and side-effect potential have all been identified as variables that affect adherence (Rand 2005; Winnick et al. 2005; Apter et al. 1998, 2003). Patients' perception of their illness and treatment also clearly account for variability in adherence behavior. In one conceptualization, patients weigh their assessment of a medication's *necessity* against their *concerns* about it; adherence improves with the degree that the former exceeds the latter (Horne and Weinman 1999). Regardless of physician instructions, patients' beliefs about their illness and their requirement for medication are strongly correlated with their adherence motivation (Bender and Bender 2005).

Treatment characteristics can also influence adherence. Treatments that are easier to take and are better accepted by patients, and thus invite improved adherence. As treatment regimens call for more than two medication doses daily, adherence declines. A dramatic drop in adherence was observed at higher dosing frequencies in a study that randomized epileptic patients receiving the same oral tablet anti-seizure medication into four daily dosing groups – qd, bid, tid, and qid. Adherence decreased to 87, 81, 77, and 39%, respectively, with dramatically decreased adherence when dosing requirements reached four times daily (Cramer et al. 1989).

There is evidence that asthma patients prefer oral to inhaled medications, and that this preference may result in greater adherence with oral medication. In the current review, we sought to assess the collective evidence regarding patient preference for, and adherence to, oral medications in contrast to inhaled medications for asthma. We therefore searched for all randomized controlled trials, meta-analyses, case-control, and cohort studies in which asthma medication adherence or preference were measured and contrasted between these two classes of medications.

Approach

Criteria for studies to be included in this systematic review were as follows:

1. Address adherence/compliance/persistence with any leukotriene antagonist, theophylline, ICS, or oral corticosteroids.
2. Contrast adherence/compliance/persistence with multiple controller medications, including oral and inhaled medication.
3. Include a measure of adherence/compliance/persistence or satisfaction.
4. Include data from a pharmacy database, RCT, meta-analysis, case-control, cohort, or observational study.

The following databases and Boolian search strategies were used to find articles related to asthma-therapy-adherence and drug-delivery-methods: MEDLINE (1966 to July Week 3 2005); HealthSTAR (1966 to June 2005); and Cumulative Index to Nursing & Allied Health Literature (CINAHL, 1982 to July Week 4 2005). Citations were identified using the following National Library of Medicine's "Medical Subject Headings" and truncated text-words, located in the title and/or abstract of the article ("exp" in front of a Medical Subject Heading retrieves its narrower terms):

> (attitude to health/OR health knowledge, attitudes, practice/ OR patient acceptance of health care/OR patient compliance/OR patient participation/OR patient satisfaction/OR treatment refusal/OR sick role/OR patient dropouts/OR health behavior/OR patient education/) OR [(patient$) 2-word adjacency (prefer$ OR adher$ OR complian$)] OR (non-adher$ OR non-complia$) AND (exp dosage forms/OR exp drug delivery systems/OR exp drug administration routes/OR exp pharmaceutical preparations/OR prescriptions, drug/OR drug administration schedule/OR exp aerosols/OR exp "nebulizers and vaporizers"/OR self administration/OR self medication/)OR [(dose$ OR dosing OR dosages$ OR medications$ OR drug$) 2-word adjacency (characteristic$ OR frequenc$ OR form$)] OR (inhal$ OR nebuliz$ OR spray$) OR (drug delivery) AND exp asthma/(as a major topic) AND English AND human.

The following additional databases were also employed to identify articles related to asthma-therapy-adherence and drug-delivery-methods: Cochrane Database of Systematic Reviews (third Quarter 2005); ACP Journal Club (1991 to May/June 2005); Database of Abstracts of Reviews of Effects (second Quarter 2005); Cochrane Central Register of Controlled Trials (third Quarter 2005); Allied and Complementary Medicine (AMED, 1985 to July 2005); International Pharmaceutical Abstracts (1970 to July 2005); and PsycINFO (2000 to July Week 4 2005).

Citations were identified using the following search strategy:

(comply or complian$ or adher$ or refus$ or dropout$ or non-adher$ or non-compl$) AND asthma$.

Reference lists in each obtained article were searched for additional relevant articles not identified through the database search. The following information was abstracted from articles meeting inclusion criteria: study population, number of subjects, study design, study duration, outcome measures, and results. Additionally, the scientific quality of each article was rated using the criteria of Harbour and Miller (2001).

Although "adherence" and "compliance" are used interchangeably in the published literature, the term adherence has been adopted here. Adherence is generally defined as the amount of medication divided by the amount prescribed. Some of the identified studies provided this information expressed as percent adherence whether the amount of medication used was measured through electronic device (Krishnan et al. 2004) or self report (Bukstein et al. 2003b) in prospective studies, or as days or doses of medication filled in pharmacy claims studies (Dorais et al. 2005; Sherman et al. 2001). Other studies measured adherence as the percent of adherent patients (Balkrishnan et al. 2005) or mean number of refill obtained over 12 months (Bukstein et al. 2003a).

Results

Utilizing the search strategy described above and after de-duplication, 2,104 published articles were identified.

Titles from each article were reviewed. Those that clearly did not meet inclusion criteria were omitted. When criteria for exclusion for the remaining articles could not be cleanly identified in the abstracts, articles were included for full review. Following this procedure, the texts of 29 articles qualified for full review. These consisted of articles that examined adherence with, or preference for, oral or inhaled controller medication in a pharmacy database, RCT, meta-analysis, case-control, cohort, or observational study.

Twelve of the 29 articles were omitted from the final analysis because upon full review they did not meet inclusion criteria. Of these, nine included only one medication and hence allowed for no comparison between medications. Three included no measure of adherence.

Of the final 17 articles meeting inclusion criteria, 8 were pharmacy claims studies, 5 were RCTs, 2 were cohort studies, and 1 each were health maintenance organization claims or questionnaire studies (Table 7.1). All included comparisons between medications delivered orally or by inhalation. The oral medications included leukotriene antagonists (LTRA) in 12 studies, theophylline in three studies (one also including oxatomide and ketotifen), and oral corticosteroid in one study, with "tablet medication" included in a survey of medication delivery preference (Tuggey et al. 2001). Inhaled corticosteroid (ICS) medications were evaluated in 14 studies. Cromolyn sodium was included in four studies, two of which also included ICS, and "inhaler treatment" in a survey of medication delivery preference (Tuggey et al. 2001).

Regardless of study design, medication category, or method of measurement, patients expressed a preference for or used oral medications more often than inhaled medications. This difference occurred in both adult and pediatric asthma populations. In the one pharmacy claims study where mean obtained doses of montelukast did not significantly exceed ICS refills, the proportion of montelukast-adherent patients (51%) was still significantly greater than the proportion adherent with ICS (41%) (Carter and Ananthakrishnan 2003). Preference for oral medication over ICS was consistent despite considerable differences in the characteristics of theophylline, montelukast, or oral steroid. One exception to this finding documented higher self-reported adherence to oxatomide and ketotifen, but not theophylline, over ICS (Alessandro et al. 1994). Additionally, the only study examining adherence to oral and inhaled steroids found that, while mean oral adherence was higher, over time differences between the two disappeared (Krishnan et al. 2004).

Discussion

Patients appear more willing to take oral over inhaled medication for asthma. The 17 studies included in this systematic review produced a consistent picture of superior adherence with oral medication despite markedly different research designs that included RCT, cohort, retrospective pharmacy claims, and questionnaire studies. In most cases, differences were large, with some studies reporting oral medication adherence

Table 7.1 Adherence related to oral versus Inhaled medication for asthma

References	Population	Design	Duration	Outcomes measured	Key findings (with 95% CI, SD, or SEM if reported)	Scientific quality	Comment
Alessandro et al. (1994)	288 children with asthma	Prospective cohort study	30–45 days	Self-reported adherence	% fully adherent patients: Oral medications (theophylline, oxatomide, ketotifen) = 71.1% Inhaled Medications (cromolyn, beclomethasone) = 59.0%	2−	Only patient-reported data were included
Balkrishnan et al. (2005)	710 asthma patients, 2–64 years	Retrospective Medicaid claims study	12 months	Refills	% adherent patients: Montelukast = 18% Fluticasone = 9%	2−	No mean adherence data provided
Bukstein et al. (2003a)	343 asthma patients, 3–83 years	Retrospective pharmacy claims study	12 months	Refills, healthcare utilization	Means refills in 1 year: Montelukast = 5.1 Fluticasone = 3.1 No group difference in health outcomes	2+	
Bukstein et al. (2003b)	33 asthma patients, 6–11 years	RCT, open label, crossover	10 weeks	Parental self-reported adherence and preference	Mean % days of adherence: Montelukast = 96.3% Cromolyn = 79.7% Reported preference: Montelukast = 87% Cromolyn = 12%	1−	Only parent-reported data were provided;
Carter and Ananthakrishnan (2003)	141 asthma patients, 3–18	Retrospective pharmacy claims study; diagnosis confirmed by chart review	6 months	Refill adherence	Mean adherence (doses filled/prescribed): Montelukast = 71% (CI = 65–77) ICS = 67% (CI = 61–73) % adherent patients: Montelukast = 51% Fluticasone = 41%	2+	Includes pharmacy claims data only
Dorais et al. (2005)	2,529 asthma patients, 15–45 years	Retrospective pharmacy claims study	12 months	Refills	Mean adherence (days of medication obtained divided by 365) LTRA = 38 ICS = 19	2+	Includes pharmacy claims data only
Jones et al. (2003)	23,225 asthma patients, 6–55 years	Retrospective pharmacy claims study	12 months	Refills	Mean adherence (doses filled/prescribed): LTRA = 67.7%, ICS = 33.8%, LABA = 40.0%	2+	Includes pharmacy claims data only

Kelloway et al. (1994)	276 asthma patients, 12–65 years	Retrospective pharmacy claims study; diagnosis confirmed by chart review	12 months	Refills	Mean (±SD) adherence (doses filled/prescribed): Theophylline = 79 ± 34% ICS = 54 ± 43% Cromolyn = 44 ± 34%	2+	Includes pharmacy claims data only
Krishnan et al. (2004)	Adults recently discharged from asthma hospitalization	Prospective cohort study	2 weeks	Electronic measurement of inhaled and oral corticosteroid use	Mean (±SEM) adherence (doses used/prescribed) ICS = 56.5 ± 4.6% Oral steroid = 68.6 ± 4.2% Patients discontinued OCS more quickly than ICS	2+	Relatively short follow-up period
Maspero et al. (2001)	124 asthma patients, 6–11 years	RCT, open label	6 months	PEFR, self-reported adherence, symptoms, health care utilization	Reported adherence: Montelukast = 97.6% Beclomethasone = 93.0% Parents preferred montelukast No differences in PEFR, symptoms, health care utilization	1–	Only self report adherence data were used
Sherman et al. (2000)	116 children with asthma	Retrospective Medicaid pharmacy claims study	12 months	Refills	Mean adherence (doses filled/prescribed): Theophylline = 71.5% (CI=66–77) ICS = 61.4% (CI=54–74) Cromolyn = 37.6% (CI=23–53)	2–	Includes pharmacy claims data only
Sherman et al. (2001)	140 asthma patients, 1–21 years	Retrospective pharmacy claims study; diagnosis confirmed by	3–12 months	Refills	Median adherence (doses filled/prescribed): Montelukast = 59%(CI=48–65) Fluticasone = 44%(CI=35–50)	2+	Includes pharmacy claims data only
Stoloff et al. (2004)	2,511 asthma patients	Retrospective pharmacy claims study	12 months	Refills	Mean adherence (doses filled/prescribed): Montelukast = 151 (CI=141–161) Fluticasone = 64 (CI=54–74) Fluticasone+salmeterol = 55 (CI=45–65) Fluticasone+montelukast = 46 (CI=36–55)	2+	Includes pharmacy claims data only

(continued)

Table 7.1 (continued)

References	Population	Design	Duration	Outcomes measured	Key findings (with 95% CI, SD, or SEM if reported)	Scientific quality	Comment
Tuggey et al. (2001)	715 asthma patients, less than 60 years	Mail questionnaire		Medication preferences surveyed	58% of respondents preferred tablets over inhaled medications	2–	Since only half of those surveyed responded, results are likely to be biased
Volovitz et al. (2000)	254 asthma patients, 6–11 years	RCT, open label	4 weeks	Medication preference and adherence, measured by parent self-report	% Preference: Montelukast = 88% Cromolyn = 12% Mean days of full adherence: Montelukast = 98% Cromolyn = 78% Beta-agonist use was lower in the Montelukast group	2–	Only self report adherence data were used; relatively short follow-up period
Weinberg and Naya (2000)	132 asthma patients, 12–17 years	RCT, open label	4 weeks	Preference measured by questionnaire	% preference: Zafirlukast = 79% Beclomethasone = 27%	2+	No behavior or disease outcome measured

Scientific quality (based upon Harbour and Miller 2001)

1–: Meta-analyses, systematic reviews or RCTs, or RCTs with a high risk of bias

2+: High quality systematic reviews of case-control or cohort studies or high quality case-control or cohort studies with a very low risk of confounding, bias, or chance and a high probability that the relationship is causal

PEFR peak expiratory flow rate, *SD* standard deviation, *SEM* standard error of the mean

2–: Case control or cohort studies with a high risk of confounding, bias, or chance, and a significant risk that the relationship is not causal.

twice that of inhaled medication (Table 7.1). While RCTs are generally held in higher regard than cohort studies when comparing drug properties, the assessment of adherence in RCTs has distinct disadvantages. Patients in RCTs are carefully selected, instructed, paid, and monitored. Their behavior, which can include medication "dumping" to create a false presentation of adherence (Simmons et al. 2000), may be markedly different from that seen in the "real world" of patient care. In this way, pharmacy claims studies have the advantage of surveying refill persistence in large groups of patients receiving routine medical care, although these studies cannot fully control other variables that may influence adherence. Prospective cohort studies can provide more accuracy in adherence assessment than pharmacy claims studies, but share with RCTs the limitations present when attempting to generalize about the larger population of asthma patients based on the behavior of a few who are willing to participate in a clinical study. It is the collective evidence across these research designs, each with particular strengths and weaknesses, that provide convincing evidence of greater adherence to oral medications.

Scientific quality of the 17 reports was variable. A total of eight retrospective studies and one RCT were rated in the category of highest qualify reflecting minimal risk of bias or confounding (Table 7.1). Areas of weakness in others included methods of data reporting, absence of a measure of variability, short follow-up period, or incomplete survey response. The single greatest limiting factor for the validity of any adherence study is frequently the method chosen to measure adherence. A large body of evidence clearly indicates that objective data are more accurate than self-reported adherence data. For example, in the study by Krishnan and colleagues (2004) patients reported an average of 85.6% adherence, while microchip-equipped metered-dose inhalers (MDIs) recorded actual adherence at 51.1%. A pediatric study similarly found about 50% adherence measured by another electronic device, while parents reported having administered more than 90% of the medicine to their children (Bender et al. 2000). Another strategy is to measure adherence by weighing the MDI canister before and after study visits and calculating number of doses emptied from the canister during the ensuing interval. This approach, which is somewhat less accurate than attaching an electronic device to a MDI (Krishnan et al. 2004; Bender et al. 2000), is nonetheless more objective and accurate than patient self-report, and is likely similar to pharmacy claims data in that both provide a gross measure of the amount of medication used but cannot discriminate doses accidentally discharged or lost in test puffs. No electronic measure can be introduced into a study without recruitment, informed consent, and study visits; hence, pharmacy refill claims remain the single most accurate method of measuring adherence in a large population of patients. Three of the reviewed studies used patient self report exclusively as the measure of adherence, which likely accounts for reports beyond the 95% adherence level (Bukstein et al. 2003a; Maspero et al. 2001; Volovitz et al. 2000). Given the likelihood that patient over-reporting of adherence was equally applied to oral and inhaled medication, the evidence of relative greater adherence to oral medications found in these studies is probably accurate even though the absolute levels of adherence are not.

Preference for oral medication in pharmacy claims and cohort studies may be confounded with dosing frequency. Specifically, oral medications are typically administered once daily and inhaled medications twice daily. Hence, it remains possible that greater adherence with oral medications reflects increased willingness to take a once-a-day (QD) medication over a twice-daily (BID) medication. However, most evidence indicates that within each medication category, there is little if any difference between QD and BID dosing for oral or inhaled medication. A comprehensive review of tablet adherence studies found similar mean adherence at once-daily (74%) and twice-daily (70%) medication, but both were dramatically higher than three (53%) or four (42%) doses per day (Greenberg 1984). Two studies of inhaled medications reported greater adherence when dosing was reduced from four to two doses (Coutts et al. 1992; Mann et al. 1992; Malo et al. 1995), but others found no dosing-related adherence difference (Gibson et al. 1995; Purucker et al. 2003; Bosley et al. 1994) and none have demonstrated clearly better adherence at QD over BID dosing. Thus, most evidence suggests that preference for oral over inhaled medications is not based on dosing frequency.

Summary

Adherence to oral medications is greater than adherence to inhaled controller medications in both adults and

children with asthma. This finding was consistent across study designs using contrasting measures of adherence, over varied time periods, but including many with 12-month follow-up, and with patients who knew they were being monitored as well as those included in an anonymous database. When directly surveyed, patients expressed preference for oral over inhaled medication. Indirect evidence suggests that patient's preference for oral medication is not related to dosing frequency.

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