Adherence to Clocortolone Pivalate Cream 0.1% in a Pediatric Population With Atopic Dermatitis

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Topical corticosteroids are first-line treatments for atopic dermatitis (AD) and their efficacy is well-established in randomized controlled clinical trials. When corticosteroids fail in clinical practice, it often is attributed to nonresponse. However, poor adherence also should be considered. With the advent of electronic monitoring systems, objective data on adherence can be obtained. The purpose of this study was to determine both self-reported and actual adherence to clocortolone pivalate cream 0.1% in the treatment of AD in a pediatric population. Six participants completed the 4-week study. Self-reported adherence was significantly higher than objectively measured adherence (P=.01). In general, adherence was best during the first week of treatment and tapered off thereafter. Clocortolone pivalate cream 0.1% was generally effective, with rapid improvement over the first week of treatment, even when adherence was limited. This study was limited by the small sample size and the failure of 2 participants to complete the study.

Patients overestimate their adherence behavior. While some patients are adherent to treatment, others rapidly discontinue their use of medication over time. Midpotency topical corticosteroids such as clocortolone pivalate cream 0.1% are highly effective treatments for AD. Poor adherence should be considered when AD is not responding to topical corticosteroid treatment.

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Atopic dermatitis (AD) affects an estimated 5% to 20% of the pediatric population and 10% to 20% of the general population[1-3]; its prevalence is increasing.[4-6] Topical corticosteroids are the mainstay of treatment for AD, reducing both itching and erythema and, consequently, decreasing the itch-scratch cycle. Because AD is a chronic condition, many patients use medications for extended periods of time and inevitably miss doses. In chronic conditions such as hypertension and diabetes mellitus, the impact of patient behaviors related to medication use, which in turn affects outcomes, has been well-documented. However, in chronic dermatologic conditions, especially those conditions with topical medications as the mainstay of treatment, there is a lack of empiric studies on patient adherence.[7]

Medical adherence is the willingness and ability of a patient to follow medication prescription guidelines and to attend medical appointments when scheduled.[8] In many cases, nonadherence rather than nonresponse is the underlying precursor of treatment failure, especially when efficacy of medication has been substantially proven.[9,10]

Traditional measures of assessing adherence, such as patient interviews, questionnaires, surveys, and diaries, are unreliable.[11] In the wake of these subjective patient responses, many researchers have shifted to the use of biologic and chemical markers to measure adherence. These serum markers may not represent valid information about daily steady state

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concentrations; moreover, it is not feasible for serum markers to measure topically applied therapies.[12]

Objective adherence assessments can be determined by technological advancements such as an electronic medication event monitoring system (MEMS®), which uses microprocessors to measure and record vital data such as the date and time of medication events. A microprocessor is placed in the cap of a standard medication bottle and records each date and time the bottle is opened as well as the interval since the last bottle opening.[13]

Preliminary data obtained from a pilot study in 10 adults with psoriasis showed that nearly 26% (33/129) of self-reported doses on the treatment logs were not verified by electronic monitoring systems.[14] Electronic monitoring systems reveal that although patients typically do take their medication, the intervals between doses can be somewhat longer than prescribed, ranging from hours to days and sometimes weeks.

Methods

Ten participants were enrolled from the Dermatology Clinic at Wake Forest University School of Medicine, Winston-Salem, North Carolina. There were no advertisements to recruit participants for this study. Eligibility criteria included any male or female aged 6 months to 25 years with a diagnosis of mild to moderate AD. Individuals with AD affecting more than 5% and less than 90% total body surface area were eligible for enrollment.

Participants and their parents/guardians (if participants were younger than 18 years) were told the study's focus was to see how well the commonly prescribed and used topical corticosteroid worked for their AD. Participants were instructed to use the medication twice daily and to use the smallest amount to cover the affected areas, excluding the face or groin. They were told their use of medication would be monitored and they were asked to record in a logbook each time the medication was applied. The participants were not told that there would be other means of monitoring their medication use besides the self-reported logs. At the final study visit, the adherence monitoring with an electronic device was disclosed and the results of each participant's adherence data were discussed. Adherence results were presented in a nonjudgmental and nonthreatening format to the participants as a group so individuals who did not have good adherence would not feel singled out. The protocol was approved by the Wake Forest University School of Medicine Institutional Review Board.

Clocortolone pivalate cream 0.1% was provided in the original manufacturer's tube with an MEMS device fitted into the cap. This microprocessor records the date and time the medication is opened for at least 3 seconds, and the data are downloaded onto software for analysis. Medication was provided at no cost to participants.

The study consisted of a 4-week treatment phase with visits at baseline and weeks 1, 2, and 4. A feedback session also was provided at the conclusion of the study to disclose use of the MEMS device and provide counseling to both the participants and the parents/guardians on individual adherence behaviors.

Severity was assessed each week using the eczema area and severity index (EASI), the investigator global assessment (IGA), and the target lesion score. Each participant's logbook was monitored and responses were recorded at each visit. Objective means for monitoring adherence at each visit were 2-fold. Participants were asked to bring their medication to each visit so it could be weighed and the amount used assessed in perspective to body surface area involvement. Additionally, data from the MEMS device were downloaded at each visit. Medications were refilled as needed at each visit and adverse events monitored.

At week 4, participants were asked to complete both admitted nonadherence and risk for nonadherence surveys. These surveys were administered at the completion of the study to avoid influencing adherence behaviors.

Data from the MEMS device were analyzed using PowerView software. Based on the study protocol, predetermined values were assigned for the prescribed number of doses, the prescribed doses per day, and the prescribed interval between doses. The MEMS device provides the unknown variables, including the number of doses taken, the doses taken per day, and the interval between doses. From these data, the percentage of correct doses, the percentage of days with correct dosing, and the percentage of correct intervals between doses were calculated.

Results

Ten participants were initially enrolled in the study. Two participants did not return after the baseline visit, at which time the medication was dispersed. Therefore, data were only available for 8 participants. Of the 8 participants, 6 completed the study. Two participants were lost to follow-up after week 2.

Although individuals up to 25 years of age were eligible to participate in the study, the oldest participant enrolled was aged 17 years (mean age, 7.9 years). The original intent of this study was to monitor adherence in both pediatric and adult populations; however, after enrollment was completed, the focus shifted to adherence in a pediatric population.

Overall, the participants had a significant response to clocortolone pivalate cream 0.1%, with an overall change in EASI of 47.7%, a 31.6% reduction in IGA, and a 43.7% reduction in target lesion score (EASI, *P*=.002; IGA, *P*=.026; target lesion score, *P*=.009). Overall actual adherence ranged from 18% to 109% (one participant used the medication on average more than 2 times per day). Adherence was highest in the first week of the study, with levels of adherence decreasing in successive weeks. Only 2 participants had an adherence level at weeks 2 or 4 that was greater than week 1.

The range of overall self-reported adherence was 71% to 97%. Self-reported adherence was

Mean Adherence and Clinical Outcome Data Compiled From 8 Participants[a]

	Baseline	Week 1	Week 2	Week 4
Medicine weight used/expected weight used, %		22	15	23
EASI	5.40	2.68	2.31	2.84
IGA	2.50	1.88	1.86	1.71
Target lesion score	1.35	0.79	0.71	0.76
MEMS® adherence, % of ideal		88	67	70
Self-reported adherence, % of ideal		92	86	87

Abbreviations: EASI, eczema area and severity index; IGA, investigator global assessment; MEMS, medication event monitoring system.
[a]Two participants were lost to follow-up after week 2.

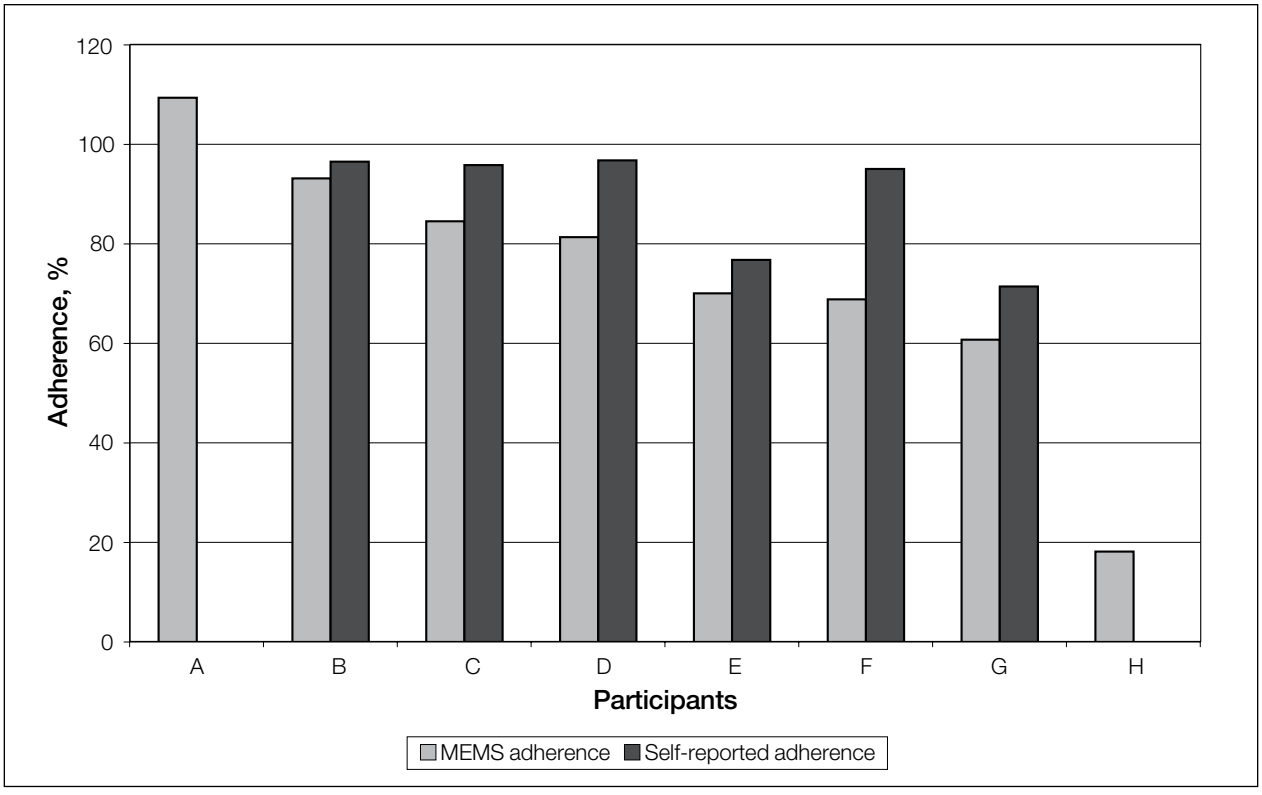

Figure 1. Overall self-reported adherence versus medication event monitoring system (MEMS®) adherence. Self-reported adherence was determined from participants' daily treatment logs. Objective measurement of adherence was assessed using an MEMS. Participants overreported their actual use of medication (*P*=.01). Two participants were lost to follow-up after week 2.

always greater than actual adherence (Table) (Figure 1). Of the 6 participants who completed their daily treatment logs, there was a significant difference between the self-reported adherence compared with the actual adherence recorded by the MEMS device (P=.01).

Overall, when participants administered their medication or had it applied by a parent or guardian, as with infants and younger children, the amount of medication used was comparable. However, the interval between applications varied.

Several participants had noteworthy trends. Participant C had an overall actual adherence of 84%, with a self-reported adherence of 96%. At week 1, participant C had an actual adherence of 93% (Figure 2). After one week of being adherent, the EASI decreased from 12.50 to 8.45. During the second week, participant C was less adherent (though self-reported adherence continued to be high), with an actual adherence of 86%. However, the EASI for week 2 continued to decrease to 4.25. Between weeks 2 and 4, adherence decreased to 57%, and at the final visit, the EASI had almost increased back to baseline, with a score of 11.25. The overall change in EASI from baseline to end of study (week 4) was 10%.

Participant E had an overall self-reported adherence of 77%, with an actual adherence of 70%. Participant E, with self-reported adherence lower than actual adherence at weeks 3 and 4, was the only one with self-reported adherence less than actual adherence during any point in time. Between weeks 3 and 4, participant E recorded less use of medication than actual use revealed (Figure 3). Participant E had an overall 32% decrease in EASI from baseline to week 4 (3.1 and 2.1, respectively). Participants F, G, and H all had lower overall actual adherence with more improvement in EASI score than participant E (Figure 4).

Increased adherence coincided with greater EASI improvement between baseline and week 4 (Figure 4)(Spearman rank correlation=0.39; P=.38). This relationship was particularly strong when adherence during week 1 was correlated with greater EASI improvement during week 1 (Figure 5) (Spearman rank correlation=0.83; P=.01).

Comment

Before the advent of objective means of measuring adherence, guessing patient compliance was no better than a coin toss.[15] With electronic monitoring systems, new understanding of patient adherence is beginning to emerge. Urquhart[13] developed a rule of sixes that is a useful approximation of what to expect of patient adherence to drugs when recorded by an electronic monitoring system. One-sixth of patients take the drug as prescribed with strict punctuality, one-sixth of patients take nearly every dose of the drug but with some variation in dose timing, one-sixth of patients occasionally miss a single day's dose with variations of dose timing, one-sixth of patients have a drug holiday 3 to 4 times a year (drug holiday implies missing all doses of a drug for 3 consecutive days) with occasional omissions of 1 to 2 doses, one-sixth of patients have a drug holiday monthly with frequent omissions of 1 to 2 doses, and one-sixth of patients take few or no doses while inevitably reporting excellent compliance.[13] Although our study was too small and the duration was too short to apply the rule of sixes, we identified a range of different adherence behaviors in the AD participants treated in this study.

Patients overestimate their adherence. Using 80% adherence as the criterion for good adherence, half of our participants were nonadherent.[16] Although 80% had been deemed an acceptable level of adherence in previous studies, this does not necessarily correlate with full effectiveness of a drug. Dosing of many prescription drugs allows for "drug forgiveness," meaning that prescribed intervals for dosing overlap one another. Therefore, patients can miss 1 or 2 doses of a prescribed drug and have no clinically apparent findings because the drug is "forgiving."[16] We found that clocortolone pivalate cream 0.1% was effective for AD, even in participants using much less than 80% of the recommended doses. The forgiving nature of midpotency topical corticosteroid treatment of AD permits effectiveness in a broad range of patients, despite poor adherence.

One participant in our study (participant C) appeared nonresponsive to treatment. For other patients, failure to improve is probably related to poor adherence. If poor adherence is not recognized, care may be escalated by adding an additional first-line agent, by combining a first-line and second-line agent, or by switching completely to a second-line agent.[17]

Adherence decreases once improvement is achieved. Patients with improved symptoms may feel less urgency to continue to treat their chronic condition. All but 2 of our participants were most adherent in the first week of the study. This decreasing trend of adherence during the short study is probably a larger issue with long-term treatment of patients with chronic conditions and may account for observations of tachyphylaxis to topical corticosteroids. On the other hand, the tendency for adherence to decrease over time and as disease improves likely limits the adverse events associated with these medications.

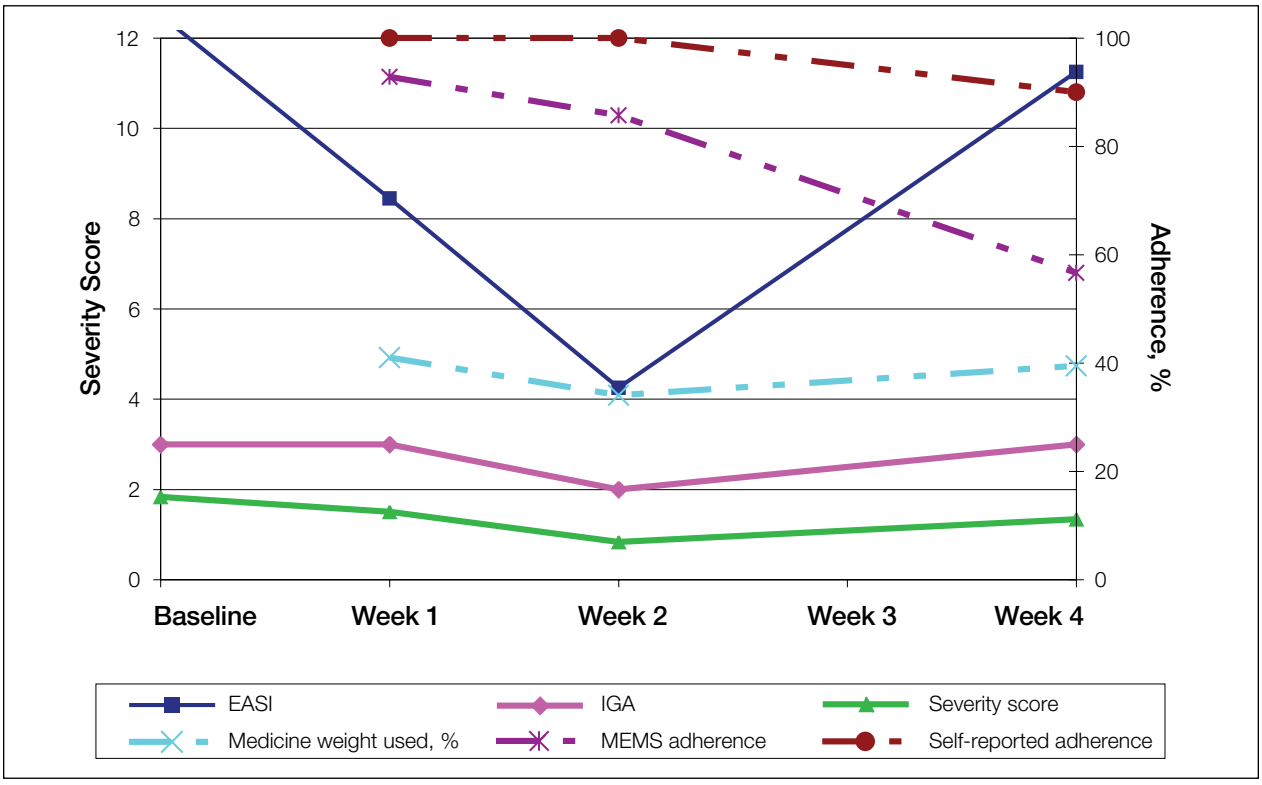

Figure 2. Participant C exhibited high levels of actual adherence initially and good improvement in disease severity over the first 2 weeks of the study. At week 4, however, the atopic dermatitis worsened and adherence decreased. EASI indicates eczema area and severity index; IGA, investigator global assessment; MEMS®, medication event monitoring system.

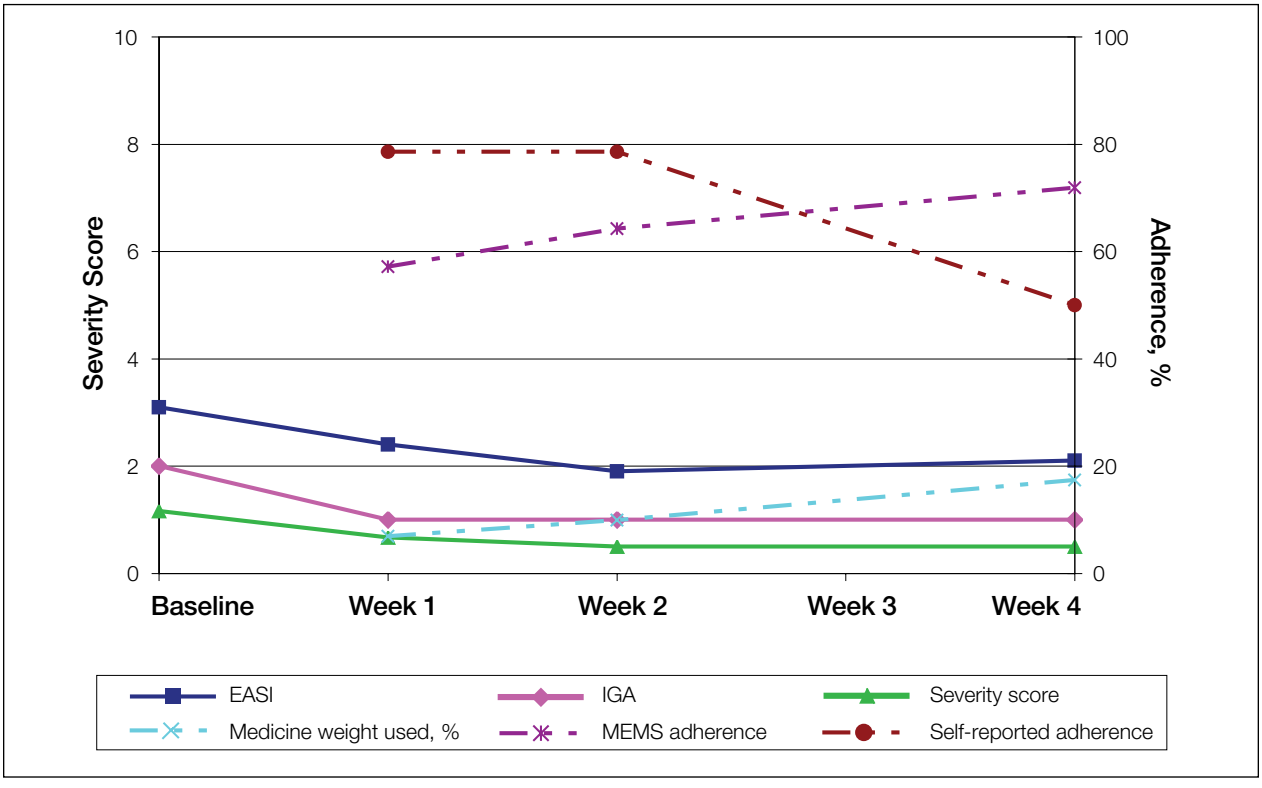

Figure 3. Participant E exhibited moderately good actual adherence throughout the study and an excellent response to treatment, despite less than 80% adherence. EASI indicates eczema area and severity index; IGA, investigator global assessment; MEMS®, medication event monitoring system.

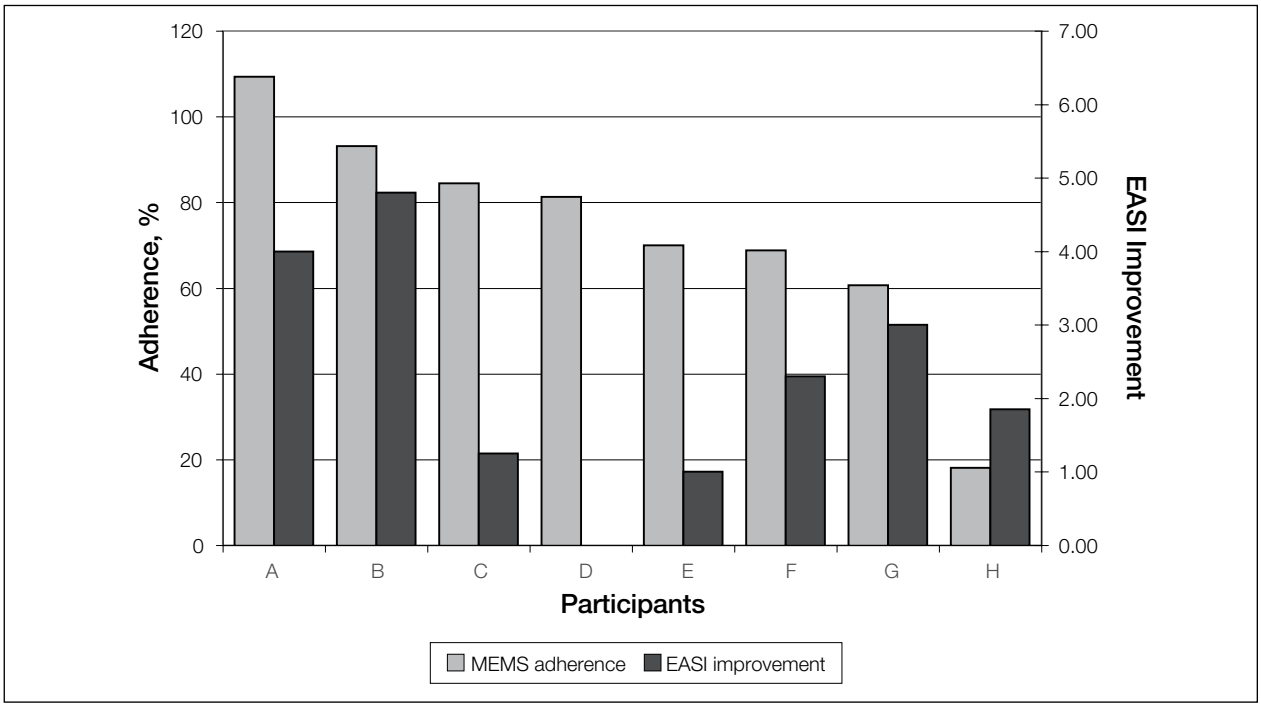

Figure 4. Overall medication event monitoring system (MEMS®) adherence versus improvement in eczema area and severity index (EASI) score (baseline to week 4). Increased adherence was descriptively associated with greater EASI improvement (Spearman rank correlation=0.39; *P*=.38). Some participants with relatively low levels of adherence exhibited smaller responses but better percentage improvement in EASI levels (participants F, G, H). Only one participant appeared to be nonresponsive to the medication when it was actually used (participant C). EASI datum is missing for participant D.

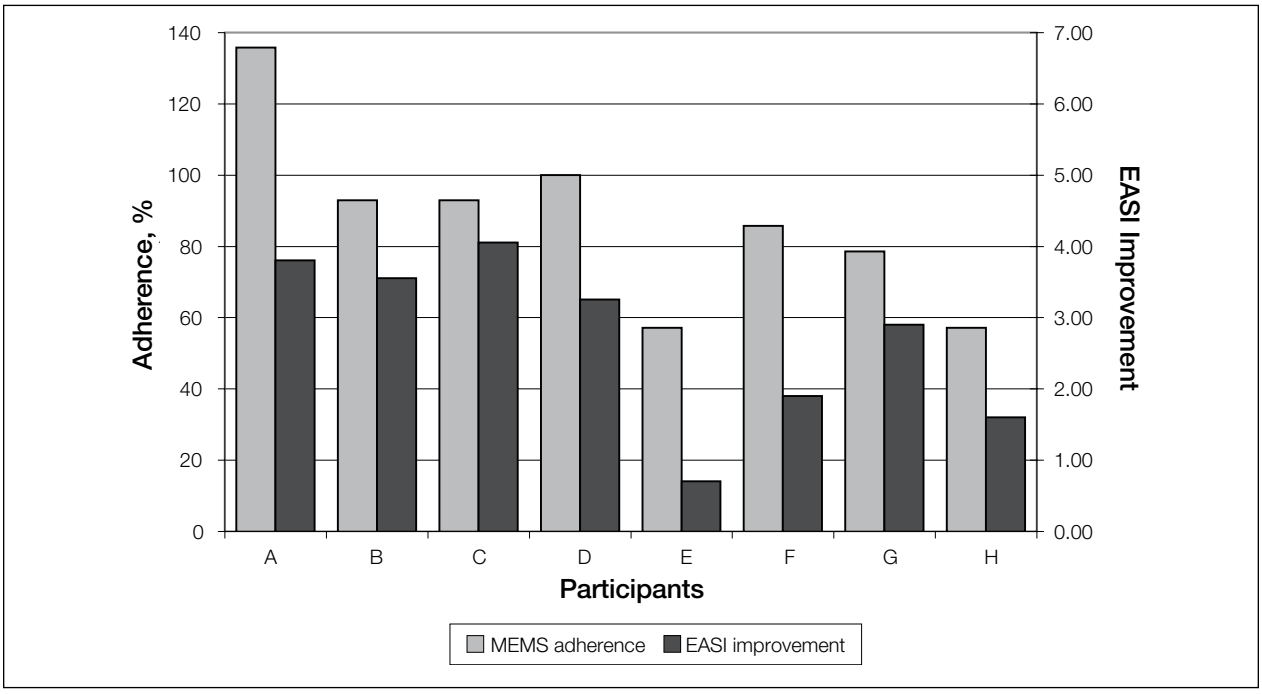

Figure 5. Medication event monitoring system (MEMS®) adherence at week 1 versus improvement in eczema area and severity index (EASI) score (baseline to week 1). Initial adherence may be a better predictor of outcome than overall adherence because patients may become less adherent as their atopic dermatitis improves. There was a strong correlation between initial adherence and improvement in EASI during week 1 (Spearman rank correlation=0.83; *P*=.01). Overall adherence is probably not as good an indicator because after patients improve in the first week, they tend to reduce their use of medication, which makes it look like decreased adherence is associated with better outcome.

A limitation of this study is that it is a study rather than an assessment of actual patients. In a previous study conducted on the use of topical medications in actual patients with AD, MEMS devices and weights of the medication were used to monitor adherence, with no subjective means of monitoring adherence. In this 8-week study of 26 patients, the mean adherence from baseline to completion of the study was 32%.[18] In our study in which participants knew they were being monitored, overall adherence was much greater, likely due to differences in patient population, return visit frequency, monitoring, and other differences that promote greater adherence in clinical trials compared with clinical practice.

Other factors that affect medication adherence in children include parental involvement, multiple caregivers being involved in care, family stability, and the attitude of both the child and caregiver toward treatment. The patients' caregivers were essential in this study because they applied the medication and recorded the doses given. Patients inevitably overestimate adherence to medication. Daily treatment logs are not a true reflection of medication usage as recorded by an MEMS device inserted into the cap of medication. Patient adherence is essential to successfully provide treatment, especially in chronic relapsing conditions such as AD.

REFERENCES

1. Laughter D, Istvan JA, Tofte SJ, et al. The prevalence of atopic dermatitis in Oregon schoolchildren. *J Am Acad Dermatol*. 2000;43:649-655.
2. Williams H, Robertson C, Stewart A, et al. Worldwide variations in the prevalence of symptoms of atopic eczema in the International Study of Asthma and Allergies in Childhood. *J Allergy Clin Immunol*. 1999;103:125-138.
3. Odom RB, James WD, Berger TG. Atopic dermatitis. In: Odom RB, James WD, Berger TG, eds. *Andrews' Diseases of the Skin: Clinical Dermatology*. 10th ed. Philadelphia, PA: WB Saunders; 2005:69-77.
4. Schafer T, Ring J. Epidemiology of allergic diseases. *Allergy*. 1997;52:14-22.
5. Schultz LF. Atopic dermatitis: an increasing problem. *Pediatr Allergy Immunol*. 1996;7:51-53.
6. Leung DY, Tharp M, Boguniewicz M. Atopic dermatitis. In: Freedberg IM, Eisen AZ, Wolff K, et al, eds. *Fitzpatrick's Dermatology in General Medicine*. 5th ed. New York, NY: McGraw-Hill; 2005:1464-1480.
7. Koehler AM, Maibach HI. Electronic monitoring in medication adherence measurement. implications for dermatology. *Am J Clin Dermatol*. 2001;2:7-12.
8. Murphy J, Coster G. Issues in patient compliance. *Drugs*. 1997;54:797-800.
9. Eisen SA, Woodward RS, Miller D, et al. The effect of medication compliance on the control of hypertension. *J Gen Intern Med*. 1987;2:298-305.
10. Paterson DL, Swindells S, Mohr J, et al. Adherence to protease inhibitor therapy and outcomes in patients with HIV infection. *Ann Intern Med*. 2000;133:21-30.
11. Urquhart J. Role of patient compliance in clinical pharmacokinetics: a review of recent research. *Clin Pharmacokinet*. 1994;27:202-215.
12. Cramer JA, Scheyer RD, Mattson RH. Compliance declines between clinic visits. *Arch Int Med*. 1990;150:1509-1510.
13. Urquhart J. The electronic medication event monitor. lessons for pharmacotherapy. *Clin Pharmacokinet*. 1997;32:345-356.
14. Balkrishnan R, Carroll CL, Camacho FT, et al. Electronic monitoring of medication adherence in skin disease: results of a pilot study. *J Am Acad Dermatol*. 2003;49:651-654.
15. Turner BJ, Hecht FM. Improving on a coin toss to predict patient adherence to medications. *Ann Intern Med*. 2001;134:1004-1006.
16. Urquhart J. Pharmionics: research on what patients do with prescription drugs. *Pharmacoepidemiol Drug Saf*. 2004;13:587-590.
17. Urquhart J. The odds of the three nons when an aptly prescribed medicine isn't working: non-compliance, non-absorption, non-response. *Br J Clin Pharmacol*. 2002;54:212-220.
18. Krejci-Manwaring J, Tusa MG, Carroll C, et al. Stealth monitoring of adherence to topical medication: adherence is very poor in children with atopic dermatitis. *J Am Acad Dermatol*. 2007;56:211-216.