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A Method to Calculate Adherence to Inhaled Therapy that Reflects the Changes in Clinical Features of Asthma

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Abstract

Rationale: Currently, studies on adherence to inhaled medications report average adherence over time. This measure does not account for variations in the interval between doses, nor for errors in inhaler use.

Objectives: To investigate whether adherence calculated as a single area under the (concentration-time) curve (AUC) measure, incorporating the interval between doses and inhaler technique, was more reflective of patient outcomes than were current methods of assessing adherence.

Methods: We attached a digital audio device (INhaler Compliance Assessment) to a dry powder inhaler. This recorded when the inhaler was used, and analysis of the audio data indicated if the inhaler had been used correctly. These aspects of inhaler use were combined to calculate adherence over time, as an AUC measure. Over a 3-month period, a cohort of patients with asthma was studied. Adherence to a twice-daily inhaler preventer therapy using this device and clinical measures were assessed.

Measurements and Main Results: Recordings from 239 patients with severe asthma were analyzed. Average adherence that was based on the dose counter was 84.4%, whereas the ratio of expected to observed accumulated AUC, actual adherence, was 61.8% (P < 0.01). Of all the adherence measures, only adherence calculated as AUC reflected changes in asthma quality of life, β-agonist reliever use, and peak expiratory flow over the 3 months (P < 0.05 compared with other measures of adherence).

Conclusions: Adherence that incorporates the interval between doses and inhaler technique, and calculated as AUC, is more reflective of changes in quality of life and lung function than are the currently used measures of adherence.

Clinical trial registered with www.clinicaltrials.gov (NCT 01529697).

Keywords: asthma; inhaler; adherence; clinical outcomes

Electronic monitors are considered the gold standard for objectively quantifying adherence to inhaled therapy (1). Most studies using electronic recording devices have reported adherence as the mean adherence, or the mean daily dose, over the study period (2–4). However, this method does not reflect variations in the way that patients use their treatments. For example, the mean adherence is the same whether an individual took the medication according to the prescribed schedule or took all the doses in the first half of a dosing period, leaving none in the second half. Inhaler technique must be included in the
assessments of adherence because an individual may use his/her inhaler according to the dosing schedule but with incorrect technique, resulting in no medication being delivered. In this case, the average use over time is meaningless unless data on the technique of use are also incorporated into the calculation of adherence. Most electronic recording devices do not assess whether the inhaler was used correctly (5–12). Hence, there is a need to develop a method to quantify adherence that accounts for variations in dosing schedules as well as inhaler user technique.

We developed a device, INhaler Compliance Assessment (INCA), which makes a digital file each time the inhaler is used (13). Analysis of this information means that the time of use, the interval between doses, and the proficiency of the inhaler use can be assessed (13). Technique errors identified by this method include failing to prime the inhaler, dispersing the medication by exhalation into the inhaler after priming, and dose dumping (14, 15). In addition, the acoustic features of inhalation are highly reflective of objectively measured peak inspiratory flow, meaning that the device can estimate the peak inspiratory flow at each inhalation (16), (17).

The aim of this study was to test the hypothesis that by including the time of use, the interval between doses, and the inhaler technique, we could quantify adherence as an area under the curve (AUC) and, furthermore, determine whether adherence calculated using AUC was more reflective of patient outcomes than the current methods of assessing adherence. Some of the results of this study have been reported previously in the form of an abstract (18).

Methods
Study Design
Patients for this study were prospectively recruited from five specialty asthma clinics in Ireland from January 2011 to December 2015. Participants included in this analysis include all patients with asthma studied to date, both those who participated in the pilot preliminary study (n = 32) and those from the single, blind, prospective, multicenter, randomized controlled clinical trial (n = 207) that followed. The full protocol of the study has already been published (19). All patients from both groups of the randomized control trial were combined to provide at least 6,000 audio files for analysis (50% of prescribed inhalations over the month for 200 patients).

On enrolment, the patients were shown how to use the inhaler, and errors were corrected using a 10-point checklist inhaler proficiency score (20–22). Over the following months (4, 8, and 12 wk), the patients returned to the clinic, where inhaler technique was checked and improved if necessary, and adherence was encouraged.

The primary end point of this study was to describe inhaler adherence using a new method of calculating adherence and its relationship with clinical outcomes in asthma, such as quality of life, disease control, and lung physiology.

Participants
Inclusion criteria were patients who were >18 years of age who had already been prescribed therapy equivalent to step 3 or higher in the Asthma Management Guidelines (23, 24) and who, in addition, had had at least one exacerbation treated with systemic glucocorticoids in the previous year. The dose of inhaled corticosteroid and long-acting β-agonist was not changed during the study. Exclusion criteria included an unwillingness to participate in a clinical study or prior hypersensitivity to salmeterol/fluticasone. Asthma diagnosis was made using a clinician diagnosis supported by one or more of the following: obstructive spirometry with at least 12% reversibility, a positive bronchial provocations challenge, or variability in the diurnal peak expiratory flow (PEF) of >15%. All patients provided written informed consent. The study was approved by local hospitals’ ethics committees.

Electronic Adherence Monitor
We have reported previously the development and validation of the INCA audio recording device in 60 patients with a total of 1,200 audio recordings (13). The device contains a microphone, internal clock, battery, and memory card with plastic housing. It is attached to an inhaler and records the audio associated with an individual using his/her inhaler (Figure 1). In previous studies, we have shown that

Figure 1. Photograph of the INhaler Compliance Assessment (INCA) device attached to a salmeterol/fluticasone Diskus inhaler. The device contains a microphone, an internal clock, a memory card, and some circuitry. Every time the inhaler device is opened, the INCA starts recording audio of the patient using his/her inhaler with a date-time stamp.
Figure 2. Calculation of adherence algorithm. Examples of patients prescribed a medication twice daily for 30 days are shown. Column A is an example of a patient with perfect adherence over a 30-day period. Attempted adherence, f(\text{AT})$, is perfect, 60 doses taken over 30 days. There were no missed doses.
inhaler errors such as low inspiratory flow and exhalation into the inhaler are identified easily. We have also shown that the acoustic features of inhalation are directly proportional to peak inspiratory flow (14, 16, 17). The device has a failure rate of <2%; it was developed at the Trinity Centre of Bioengineering, Dublin, and is Conformité Européene (CE) marked and manufactured by Vitalograph Ltd., Ennis, Republic of Ireland. The device is currently available for use in research. Participants in this analysis received an INCA-enabled salmeterol/fluticasone Diskus inhaler each month.

**Extraction of Features of Inhaler Use and Calculating Adherence**

Audio raters assessed each acoustic recording for evidence of critical errors, as described previously (13–15). Critical errors in inhaler use, such as low inspiratory flow, were classified as no dose, whereas noncritical errors, such as vertical position of the inhaler, were classified as a complete dose.

The interval between doses was calculated on the basis of drug half-life, and the measurement of doses taken was related to this drug interval (for this study, the pharmacokinetic profile and drug half-life of salmeterol were used). A dose taken within one half-life of the drug, after the previous dose, was counted as one dose. When the interval between doses was greater than one half-life and less than two half-lives, this was considered 0.5 dose. In cases in which the interval between doses was greater than four half-lives, this was considered no dose.

Information collected on the time, the interval between doses, and the technique of inhaler use was combined to calculate an AUC metric. Initially, the AUC is calculated for the expected doses, denoted by \( f(\text{ex}) \). After this, the AUC is calculated for the participant’s attempted dosing, denoted by \( f(\text{at}) \). Attempted dosing refers to the number of doses that patients attempt to take (i.e., evidence of drug priming in the acoustic analysis; these doses may be taken correctly or incorrectly) and was used to calculate the attempted adherence, \( f'(\text{AT}) \).

**Attempted adherence** \( f(\text{AT}) = f(\text{at})/f(\text{ex}) \%

This value, relative to the expected doses, \( f(\text{ex}) \), gives information on overdosing, denoted by \( f(\text{od}) \) and missed doses, denoted by \( f(\text{md}) \). By removing doses where a critical error has occurred, the actual doses, denoted by \( f(\text{ad}) \), may be deducted. Subtracting this value from \( f(\text{AT}) \) gives us the technique rate, denoted by \( f(\text{te}) \).

Technique rate \( f(\text{te}) = f(\text{AT}) - f(\text{ad}) \( \%$$

The interval adherence \( f(i) \) is calculated as the ratio of the attempted interval adherence \( f(i)\text{at} \) to the expected interval adherence \( f(i)\text{ex} \).

Interval adherence \( f(i) = f(i)\text{at} / f(i)\text{ex} \( \%$$

Furthermore, by removing the technique errors, we can calculate the actual adherence \( f(AC) \).

Actual adherence \( f(AC) = f(i) - f(\text{te}) \( \%$$

See Figure 2 for a graphical display of this process and for a definition of terms.

**Analysis of PEF**

A similar method to that described above was used to analyze PEF data. Expected PEF was calculated on the basis of age, sex, and height.

\[ \text{AM PEF AUC} = \frac{f(\text{Recorded AM PEF})}{f(\text{Expected AM PEF})} \]

PEF variability (25) was calculated as the difference between A.M. and P.M. PEF AUC.

\[ \text{AM PM variability} = \frac{f(\text{AM}) - f(\text{PM})}{f(\text{PM})} \%

**Outcome Measures**

At the end of each month, the INCA device was collected from the participant. Audio data were downloaded from each device to provide information on inhaler use for the previous month. Additional information recorded at each visit included the findings of the Asthma Quality of Life Questionnaire (AQLQ) and the Asthma Control Test (ACT), the patient’s self-reported reliever medication use, PEF, and any recent exacerbations. Change in AQLQ (26, 27) was divided into those who did (improvers) and did not (nonimprovers) have an improvement of 0.5 points (the minimal clinically important difference in AQLQ). Change in PEF was also categorized into improvers and nonimprovers on the basis of a 10% cutoff (23, 24).

**Statistical Analysis**

Descriptive statistics were used to present basic patient details for those included in this analysis. Means and SDs are presented for continuous variables, and frequencies and percentages for categorical variables.
For each patient and each month of data, the following adherence measures were calculated: dose counter (average adherence), mean daily dose, \( f_{md} \), \( f_{od} \), \( f_{at} \), and \( f_{act} \). Baseline adherence measures at Month 1 were examined initially. We used \( t \) tests to compare the means of these different adherence rates. Proportions were compared using a \( \chi^2 \) analysis. Over the 3 months, differences in adherence measures and associations with clinical outcomes were examined using an ordinary least-squares regression. Each adherence measure regression coefficient was compared with \( f_{ac} \) for improvers and nonimprovers separately. To compare these coefficients, a test of linear hypothesis after estimation was used, to determine if the linear expressions were equal.

Because there is no gold standard for calculating adherence, a sensitivity analysis was done by categorizing adherence into good and poor on the basis of an 80% cutoff for each adherence measure. With this categorization, each adherence measure’s sensitivity and specificity at identifying improvers and nonimprovers (AQLQ and PEF) and controlled and uncontrolled (ACT) are reported. All statistical analysis was conducted using Stata Release 13 (StataCorp, College Station, TX).

### Results

#### Participants

The clinical characteristics of the 239 participants included in this analysis can be seen in Table 1. The patient cohort was primarily female (62%) with a mean (SD) age of 49 (16.1) years. A large proportion of patients in this cohort had poorly controlled asthma, with a mean AQLQ of 3.9 and ACT of 12.2, and 145 patients (61%) used a short-acting \( \beta \)-agonist on a daily basis.

#### Baseline Adherence to Inhaled Therapy

In the first month, there were 11 device failures (<6%), 5 devices (<3%) were lost, and a further six patients (<3%) had missing dose counter information. For the first month, the total number of audio files with evidence of drug priming was 7,973.
compared with a total of 8,169 doses on the dose counter (correlation coefficient = 0.981). The differences between the two measures were caused by episodes of multiple priming of the inhaler without inhalation; this was recorded by the dose counter as doses were taken. The mean number of audio files per patient from the 60-dose Diskus inhaler was 48.6 ± 10.8, whereas the mean number of doses recorded from the dose counter was 49.3 ± 18.4.

Analysis of the time-stamped audio data recorded to the INCA device showed errors in inhaler handling, errors in overdosing, and errors in missed doses. The most common critical errors in inhaler use included 308 events (3.1% of all attempted doses) of low peak inspiratory flow (PIF) and 283 events (2.8% of all attempted doses) of exhalation into the device. Other errors included multiple inhalations with no breath hold and multiple priming of the inhaler without inhalation. The mean technique error rate, \( f(te) \), was 14.2 ± 21.5%. The mean overdosing rate, \( f(od) \), was 6.6 ± 9.2%, and the mean missed doses rate, \( f(md) \), was 20.7 ± 18.7%. Using the AUC method described above and accounting only for evidence of priming of the inhaler, the mean actual adherence, \( f(AC) \), was 79.4 ± 20.7%. Combined with the technique error rate, this meant that the mean actual adherence, \( f(AC) \), at 1 month was 61.8 ± 28.5%, significantly different from \( f(AT) \) (\( P < 0.01 \)) (Table 2 and Figure 3).

### Table 3. Patients considered adherent using various measures of adherence, with 80% as a cutoff for good and poor adherence

| Adherence Measure          | Good Adherence (>80%) | Poor Adherence (<80%) |
|----------------------------|------------------------|------------------------|
| n                          | Mean ± SD (%)          | n                      | Mean ± SD (%)          |
| Actual adherence \( f(AC) \) | 67                     | 90.9 ± 4.5             | 156                    | 49.3 ± 25.1             |
| Average adherence from dose counter | 153                    | 93.4 ± 12.0            | 64                     | 62.9 ± 15.6             |
| Mean daily dose            | 161                    | 94.2 ± 14.0            | 62                     | 61.1 ± 18.3             |
| Attempted adherence \( f(AT) \) | 140                    | 91.4 ± 5.4             | 83                     | 59.0 ± 21.2             |

Figure 4. Asthma quality of life (AQLQ) value was recorded on a monthly basis. The minimal clinically important improvement in AQLQ is a 0.5 increase. Patients were divided into those who had a change in AQLQ ≥0.5 over 3 months (improvers) and those with a change <0.5 over 3 months (nonimprovers). (A) Relationship between the changes in AQLQ and the average adherence calculated from the Diskus dose counter is shown. Using this method of calculation of adherence, paradoxically, nonimprovers had a higher level of adherence than did those who improved. (B) Relationship between the changes in AQLQ and the mean daily dose is shown. Nonimprovers similarly showed no relationship between adherence and change in AQLQ. (C) Relationship between the changes in AQLQ and attempted adherence is shown. Nonimprovers had a higher adherence rate, for a bigger drop in AQLQ, similar to mean daily dose; however, improvers had a better adherence rate as the improvement in AQLQ increased. (D) Relationship between the changes in AQLQ and the actual adherence is shown. Nonimprovers had low adherence rates, which increased as the fall in AQLQ decreased, and improvers had higher adherence rates, which improved as the change in AQLQ increased. There was a significant difference when comparing average adherence (dose counter) with actual adherence and average adherence with attempted adherence (\( P < 0.01 \) and \( P < 0.03 \), respectively).
counter adherence was 84.4 ± 19.1% and the mean daily dose was 85.0 ± 21.3%.

Using an 80% cutoff to indicate good adherence, 67 patients (30%) had good \( f(AC) \) over the first month of inhaler use. This was much lower than that calculated using other adherence measures (Table 3). As a result, the average adherence, using the dose counter, had 37.1% sensitivity and 93.0% specificity, with a 90.2% positive and a 46.2% negative predictive value to actual adherence, \( f(AC) \) (Table 4).

**Associations between Adherence Measures and Clinical Outcomes**

**Quality of life.** Patient-reported AQLQ change from the start of the monitoring period to the end of the study was analyzed. The coefficient of the regression line for the \( f(AC) \) was 1.1 for improvers and 2.2 for nonimprovers, both of which were significantly different from \( f(AT) \) (P < 0.01 and \( r^2 = 0.2 \) for nonimprovers) mean daily dose (P < 0.03 and \( r^2 = 0.7 \) for improvers, P < 0.02 and \( r^2 = 0.2 \) for nonimprovers), and average adherence (P < 0.03 and \( r^2 = 0.7 \) for improvers, P = 0.02 and \( r^2 = 0.2 \) for nonimprovers) (Table 5). In contrast, among those with an AQLQ <5, 35% had an \( f(AC) <80\% \) and only 16% had an average dose counter adherence <80% (P < 0.01, \( \chi^2 \) test). The sensitivity and specificity of the various measures of adherence in identifying patients with a >10% improvement in A.M. PEF are shown in Table 6.

**\( \beta \)-Agonist use.** Patients who used their short-acting \( \beta \)-agonist (SABA) every day had a mean \( f(AC) \) of 59.0 ± 30.2%, an average adherence of 83.9 ± 16.1%, a mean daily dose of 84.7 ± 19.4%, and a mean attempted adherence of 79.7 ± 19.5% (P < 0.01 when all rates were compared with \( f(AC) \)).

**Discussion**

Both electronic recording devices and manual dose counters are commonly used to assess adherence in clinical trials. Traditionally, adherence is judged to be good when the average adherence is >80% of expected use. However, there is no scientific basis for assessing adherence as an average value or that 80% adherence is a valid way of demonstrating good adherence. The purpose of this study was to review some common methods of assessing adherence and to compare these with a proposed new method. The term adherence refers to the way that a patient follows the physician's prescription, which is based on the pharmacokinetic principles of the medication. We reasoned that by using the information recorded to the INCA device, which records the time of use and the time between doses, and adjusting for the modifying effect on the dose administered caused by incorrect user technique, we could calculate adherence. To do this, we calculated medication use as an AUC metric, a measure commonly used to reflect plasma drug concentration, and we tested the relationship of this method of calculating adherence to established methods in a cohort of patients with asthma (18, 19).

Despite inhaler training, adherence education, and knowingly using an electronic recording device, and despite participating in a clinical trial focused on promoting adherence, episodes of missed doses, overuse, dose dumping, and critical errors in inhaler use were all recorded. As a result, adherence calculated in the proposed manner was significantly lower than that

**Table 4. Adherence measures compared with actual adherence**

| Adherence Measure       | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) |
|-------------------------|----------------|----------------|---------|---------|
| Average adherence       | 37.1           | 93.0           | 90.2    | 46.2    |
| from dose counter       |                |                |         |         |
| Mean daily dose         | 52.8           | 96.6           | 96.4    | 54.1    |
| Attempted adherence     | 43.0           | 97.0           | 96.2    | 49.2    |

The table presents the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of the dose counter, the mean daily dose, and the attempted adherence in correctly classifying good and poor adherence relative to the actual adherence (using the traditional 80% cutoff for good adherence).

**Table 5. Adherence rates at month 3 and their relationship with changes in AQLQ and PEF**

| Adherence Measure | PEF | AQLQ |
|-------------------|-----|------|
|                   | Improver* (%) | Nonimprover (%) | Improver† (%) | Nonimprover (%) |
| Actual adherence \( f(AC) \) | 68.5 ± 28.4 | 65.7 ± 27.6 | 66.4 ± 28.4 | 64.4 ± 27.3 |
| Average adherence from dose counter | 87.2 ± 13.0 | 89.4 ± 14.5 | 87.2 ± 13.8 | 88.6 ± 15.3 |
| Mean daily dose | 84.4 ± 13.7 | 84.0 ± 16.3 | 83.3 ± 15.2 | 83.6 ± 16.5 |
| Attempted adherence \( f(AT) \) | 81.8 ± 16.6 | 82.4 ± 18.5 | 82.1 ± 16.5 | 80.7 ± 20.2 |

* \( >10\% \) improvement in A.M. PEF readings.
† \( >0.5 \) point improvement in AQLQ.
quantiﬁed by other commonly used methods, such as mean adherence (28–31) or the mean daily dose (2, 32).

Over a 3-month period in which adherence, AQLQ, ACT, PEF, and inhaled β-agonist use were quantiﬁed, only actual adherence \(f(AC)\) reﬂected the changes in patient outcomes. In contrast, average adherences calculated from the dose counter, the mean daily dose, and the attempted adherence \(f(AT)\) all failed to distinguish between those who did and did not have clinically meaningful improvements in several related clinical measures. For example, an inverse relationship was found for nonimprovers, between the currently used measures of adherence and changes in AQLQ. In addition, PEF correlated only with \(f(AC)\), with less morning-to-evening variability in PEF associated with higher levels of \(f(AC)\).

Likewise, signiﬁcantly higher β-agonist reliever use was associated with lower \(f(AC)\). These relationships were not seen with other measures of adherence. These results demonstrate the importance of variation in the time of use and errors in inhaler handling and emphasize the need to incorporate this information into the calculation of adherence.

Limitations

This study has several limitations. First, the patients studied had already been prescribed inhaled salmeterol/fluticasone for some time. Hence, it is not too surprising that there were relatively small changes in lung function and quality of life. Furthermore, the duration of follow-up was relatively short and possibly not of sufﬁcient duration to see more signiﬁcant correlations with clinical parameters (33). Nonetheless, the novel measurement of adherence that we have described demonstrated signiﬁcant associations with several measures of asthma over the timeframe, demonstrating

| Adherence Measure | PEF | AQLQ |
|-------------------|-----|------|
|                   | Sensitivity (%) | Specificity (%) | Sensitivity (%) | Specificity (%) |
| Actual adherence \(f(AC)\) | 59.8 | 46.9 | 66.7 | 44.6 |
| Average adherence from dose counter | 19.5 | 71.9 | 19.2 | 73.7 |
| Mean daily dose | 27.1 | 69.7 | 25.0 | 73.3 |
| Attempted adherence \(f(AT)\) | 32.5 | 63.6 | 37.5 | 66.0 |

Definition of abbreviations: AQLQ = Asthma Quality of Life Questionnaire; PEF = peak expiratory flow.

Figure 5. Twice-daily peak expiratory flow (PEF) was divided into morning (A.M.) and evening (P.M.) readings. The mean variability between the A.M. and P.M. readings was calculated for each month for each patient. (A–D) Change in A.M.–P.M. PEF variability for the four measures of adherence, (A) average adherence calculated from the dose counter, (B) the mean daily dose, (C) attempted adherence \(f(AT)\) and (D) actual adherence \(f(AC)\). actual adherence \(f(AC)\) showed the most negative relationship with A.M.–P.M. PEF variability (slope, \(-0.8\)). There was a signiﬁcant difference between average adherence with both \(f(AC)\) and \(f(AT)\) \((P = 0.01 \text{ and } P = 0.03, \text{ respectively})\).
its appropriateness. Future experimental tests of the approach described here will involve testing in larger populations and for longer periods of time.

We have previously described the close relationship of acoustically assessed PIF with objectively measured PIF (14, 16, 17). We have also described the significant effect of both low PIF and that of exhalation into the inhaler on drug delivery (14, 16, 17, 34). For the purpose of calculating the impact of inhaler technique errors on adherence, we used a binary response (present/not present), but different degrees of user errors will have different impacts on drug delivery, and this will need to be further evaluated and incorporated into this method of calculating adherence (14–17). Adherence and nonadherence to an intervention has serious and obvious implications for a clinical trial. Variations in adherence influence the statistical power of a study and the effect size of different therapies and have serious implications for estimates of the incidence of adverse events. In addition, knowing the adherence of a therapy in a clinical trial can provide insight into patient acceptability of a new treatment or new inhaler device. The results of this study highlight the limited sensitivity of the currently used method of describing adherence as a mean value.

The approach for calculation of actual adherence \([\{\text{AC}\}\]\) described here would be useful for clinical trials involving a diverse range of respiratory conditions, including those requiring inhaled antibiotics or other agents, where errors in timing or user technique may directly affect drug accumulation. This may also be important in phase 2 studies in which adjustment for patients achieving per protocol adherence may help avoid type 2 errors in data analysis.

Conclusions

We have developed a method of calculating inhaler adherence modeled on the concepts of drug pharmacokinetics that incorporates both the time of use of an inhaler and the technique used. This method not only identifies which component of adherence is deficient but is also more reflective of the clinical changes expected from a medication than are the current methods used to assess adherence.

Author disclosures are available with the text of this article at www.atsjournals.org.

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