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

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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: We investigated 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 current methods of assessing adherence.

Methods: We attached a digital audio device (INCA™) 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 asthma patients were studied. Adherence to a twice-daily inhaler preventer therapy using this device and clinical measures were assessed.

Measurements and Results: Recordings from 239 patients with severe asthma were analysed. Average Adherence, 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 adherence measures, only adherence calculated as AUC reflected changes in asthma quality of life, beta agonist reliever use and PEF, over the three months (p<0.05 compared to other measures of adherence).

Conclusion: 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 the currently used measures of adherence.
Electronic monitors are considered to be the gold standard for objectively quantifying adherence (1). Most studies using electronic recording devices have reported adherence as the mean adherence or, the Mean Daily Dose, over the study period (2) (3) (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 needs to be included in the assessment of adherence because an individual may take their 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 is also incorporated into the calculation of the adherence. Most electronic recording devices usually do not assess if the inhaler was taken 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 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 other errors such as 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 accounting for 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 current methods of assessing adherence. Some of the results of this study have been previously reported 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 asthma patients studied to date, both those who participated in the pilot preliminary study (n=32) and also from the single blind prospective multicentre randomised controlled clinical trial (n=207) which followed. The full protocol of the study has already been published (19). All patients from both groups of the randomised control trial were combined to provide at least 6000 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 weeks) the patients returned to the clinic, where inhaler technique was checked and improved if necessary, and adherence encouraged.
The primary endpoint of this manuscript 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 aged ≥18 already prescribed therapy equivalent to step 3 or higher on the Asthma Management Guidelines (23,24) who, in addition, had at least one exacerbation treated with systemic glucocorticoids in the prior year. The dose of inhaled corticosteroid and long acting beta-agonist (LABA) 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 provocation challenge or variability in the diurnal peak expiratory flow (PEF) of more than 15%. All patients provided written informed consent. The study was approved by local hospitals ethics committees and registered on Clinicaltrials.gov, NCT01529697.

Electronic Adherence Monitor

We have previously reported the development and validation of the INCA™ audio recording device in 60 patients with a total of 1200 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 their inhaler, see Figure 1. In previous studies we have shown that inhaler errors such as low inspiratory flow and exhalation
into the inhaler are easily identified. We have also shown that acoustic features of inhalation are directly proportional to peak inspiratory flow (14,16,17). The device has a failure rate <2% and was developed at the Trinity Centre of Bioengineering, Dublin, is 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 previously described (13-15). Critical errors in inhaler use, such as low inspiratory flow were classified as no dose. While non-critical errors, such as vertical position of the inhaler, were classified as a complete dose.

The interval between doses was calculated based on 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 was used). In the case of a dose taken within one half-life of the drug, after the previous dose, this was counted as one dose. Where the interval between doses was greater than one half-life and less than two half-lives, this was considered as 0.5 a dose. In cases where the interval between doses was greater than four half-lives, this was considered as no dose. Information collected on the time, interval between doses and technique of inhaler use were combined to calculate an AUC metric. Initially, the AUC is calculated for the expected doses, denoted by $f(\text{ex})$. Following 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 used to calculate the Attempted Adherence, $f(\text{AT})$.

\[
\text{Attempted Adherence } f(\text{AT}) = \frac{f(at)}{f(ex)} \quad [\%]
\]

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

\[
\text{Technique Rate } f(te) = f(\text{AT}) - f(ad) \quad [\%]
\]

The Interval Adherence $f(i)$ is calculated as a ratio of the attempted interval adherence $f(iat)$ to the expected interval adherence $f(iex)$.

\[
\text{Interval Adherence } f(i) = \frac{f(iat)}{f(iex)} \quad [\%]
\]

Furthermore, by removing the technique errors we can calculate the Actual Adherence $f(AC)$.

\[
\text{Actual Adherence } f(AC) = f(i) - f(te) \quad [\%]
\]

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

**Analysis of Peak Expiratory Flow (PEF)**

A similar method to that described above was used to analyse PEF data. Expected PEF was calculated based on age, sex and height.

\[
\text{AM PEF AUC } f(AM) = \frac{f(\text{Recorded AM PEF})}{f(\text{Expected AM PEF})} \quad [\%]
\]
PEF variability (25) was calculated as the difference between AM and PM PEF AUC.

\[ AM \ PM \ Variability \ f(AMP) = f(AM) - f(PM) \ [%] \]

Outcome Measures

At the end of each month the INCA™ device was collected from the participant. Audio data was downloaded from each device to provide information on inhaler use for the previous month. Additional information recorded at each visit included the Asthma Quality of Life Questionnaire (AQLQ), 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 (non-improvers) have an improvement of 0.5 points (the minimal clinically important difference in AQLQ). Change in PEF was also categorised into improvers and non-improvers based on a 10% cut off (23,24).

Statistical Analysis

Descriptive statistics were used to present basic patient details for those included in this analysis. Means and standard deviations (SD) 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, \( f(md) \), \( f(od) \), \( f(AT) \), \( f(te) \), and \( f(AC) \). Baseline adherence measures at month 1 were initially examined. We used t-tests to compare the means of these different adherence rates. Proportions were compared employing a \( \chi^2 \) analysis. Over the three months differences in adherence measures and associations with clinical outcomes were examined using an
ordinary least squares (OLS) regression. Each adherence measure regression coefficient was compared to \( f(A_C) \) for improvers and non-improvers separately. To compare these coefficients a test of linear hypothesis after estimation was used, testing if the linear expressions are equal.

As there is no gold standard for calculating adherence a sensitivity analysis was done by categorising adherence into good and poor based on an 80% cut off for each adherence measure. With this categorisation, each adherence measure’s sensitivity and specificity at identifying improvers and non-improvers (AQLQ and PEF) and controlled and uncontrolled (ACT) is reported. All statistical analysis was conducted using Stata Release 13 (StataCorp. 2013. *Stata Statistical Software: Release 13*. College Station, TX: StataCorp LP).

**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 were poorly controlled with a mean AQLQ of 3.9, ACT of 12.2 and 145 (61%) patients used a short acting beta-agonist on a daily basis.

**Baseline Adherence to Inhaled Therapy**

In the first month there were 11 (<6%) device failures, 5 (<3%) devices were lost and a further 6 (<3%) patients had missing dose counter information. The total number of audio files, for the
first month, with evidence of drug priming was 7973, compared to a total of 8169 doses on the dose counter (correlation coefficient = 0.981). The reason for the differences between the two measures is due to episodes of multiple priming of the inhaler without inhalation; this is recorded by the dose counter as doses taken. The mean number of audio files per patient from the 60 dose Diskus™ inhaler was 48±10.8, while from the dose counter the mean number of doses recorded was 49±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 accounting only for evidence of priming of the inhaler, the mean Attempted Adherence, \( f(AT) \), was 79.4±20.7%. Combined with the technique error rate this meant that the mean Actual Adherence, \( f(AC) \), at one month was 61.8±28.5%, significantly different from \( f(AT) \), \( p<0.01 \), see Table 2 and Figure 3.

**INCA and dose counter data.** Data for both the dose counter and the INCA device was available for 217 (91%) of the 239 patients. For these patients the average dose counter adherence was 84.4±19.1% and the Mean Daily Dose was 85.0±21.3%.

Using an 80% cut off to indicate good adherence, 67 (30%) patients had good \( f(AC) \) over the first month of inhaler use. This was much lower than that calculated using other
adherence measures, see 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 46.2% negative predictive value to Actual Adherence, $f(AC)$, see Table 3.

**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 analysed. The coefficient of the regression line for the $f(AC)$ was 1.1 for improvers and 2.2 in non-improvers, which were significantly different from $f(AT)$ ($p\leq 0.01$ & $r^2=0.2$ for non-improvers), Mean Daily Dose ($p\leq 0.03$ & $r^2=0.7$ for improvers, $p<0.02$ & $r^2=0.2$ for non-improvers), and the Average Adherence ($p<0.03$ & $r^2=0.7$ for improvers, $p\leq 0.02$ & $r^2=0.2$ for non-improvers), see Figure 4.

For the purpose of this analysis, an AQLQ $\geq 5$ was considered to be indicative of a good quality of life score (26,27). At month three, both good quality of life score (AQLQ $\geq 5$) and good adherence ($\geq 80\%$) were seen in 17% of patients when adherence was calculated by the $f(AC)$ method compared to 36% when adherence was calculated using the dose counter. 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 an improvement in AQLQ is shown in Table 4.

*Lung function.* The mean (range) variability between morning and evening PEF (AM to PM variability) was 4.9% (1-90) in month 1, 5.6% (1-85) in month 2 and 5.0% (1-80) in month 3. Compared to the other measures of adherence, $f(AC)$ demonstrated the greatest correlation
to AM PM PEF variability, \( (p \leq 0.03 & r^2 = 0.3) \), see Figure 5. The sensitivity and specificity of the various measures of adherence in identifying patients with a \( \geq 10\% \) improvement in AM PEF are shown in Table 4.

**Beta-agonist use.** Patients that used their SABA every day, had a mean \( f(AC) \) of 59.0\( \pm \)30.2\%, Average Adherence of 83.9\( \pm \)16.1\%, a Mean Daily Dose of 84.7\( \pm \)19.4\% and a mean Attempted Adherence of 79.7\( \pm \)19.5\%, \( p < 0.01 \) when all rates are compared to \( f(AC) \).

**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 asthma patients (18,19).

Despite inhaler training, adherence education, knowingly using an electronic recording device and participating in a clinical trial focused on promoting adherence, episodes of missed doses, over use, 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 quantified by other commonly used methods, such as mean adherence (28-31) or the Mean Daily Dose (2,32).

Over a three-month period in which adherence, AQLQ, ACT, PEF and inhaled beta agonist use were quantified, only Actual Adherence \((f(AC))\) reflected the changes in patient outcomes. In contrast, Average Adherence 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 non-improvers, between the currently used measures of adherence and changes in AQLQ. Additionally, PEF correlated only with \(f(AC)\), with less morning to evening variability in PEF associated with higher levels of \(f(AC)\). Likewise, significantly higher beta 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 time of use and errors in inhaler handling, and emphasize the need to incorporate this information into the calculation of adherence.
Limitations

There are several limitations in this study. Firstly, the patients studied were already 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 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 non-adherence to an intervention has serious and obvious implications for a clinical trial. Variations in adherence influences the statistical power of a study, impacts the effect size of different therapies and has serious implications for estimates of the incidence of adverse events in a study. Additionally, 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 ($f(AC)$) described here would be useful for clinical trials involving a diverse range of respiratory conditions, including inhaled antibiotics or other agents, where either errors in timing and user technique may directly affect drug accumulation. This may also be important in Phase 2 studies where 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 modelled on the concepts of drug pharmacokinetics that incorporates both the time and the technique of use of an inhaler. 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 current methods used to assess adherence.
Acknowledgements

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Figure Legends

**Figure 1:** This is a photograph of the INCA™ device attached to a salmeterol/fluticasone Diskus™ inhaler. The device contains a microphone, internal clock, a memory card and some circuitry. Every time the inhaler device is opened the INCA™ starts recording audio of the patient using their 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, \( f(AT) \) is perfect, 60 doses taken over 30 days. There were no missed doses, no technique errors, and the interval between doses is within one half-life, the Actual Adherence rate, \( f(AC) \), is 1.00 (100%). Column B is an example where the medication was taken only once daily for 30 days. The Attempted Adherence, \( f(AT) \) is half that of column A and there were 30 missed doses over 30 days. In this example there were no technique errors. Due to missing doses every day the interval between doses was also poor and \( f(AC) \) is 0.50 (50%). Column C is an example of a patient who takes the medication (with no technique errors) every day, twice a day, but with erratic timing. There was perfect Attempted Adherence, with no missed doses and no technique errors. Due to the erratic time of use, some doses which have an interval beyond the half-life of the drug, \( f(i) \), the \( f(AC) \) is reduced to 0.92 (92%). Finally, column D is an example of a patient who takes the medication only once daily and makes a technique error for the first 15 days of the 30 days. Therefore, the, \( f(AT) \) is half that of expected (50%) due to missing 30 doses. There were also 15 doses with technique
errors, and due to missing doses every day the interval between doses was poor, therefore the $f(AC)$ is 0.25 (25%).

**Figure 3:** Graphical representation of adherence calculated in a number of ways. The data used for this graph is the first month’s inhaler use by a cohort of 217 (of 239) asthma patients enrolled in a prospective adherence intervention clinical study who were asked to use a dry powder inhaler twice daily. The Actual Adherence rate, $f(AC)$, is significantly different than the adherence calculated using the current methods, e.g. Average Adherence from the dose counter and the Mean Daily Dose, and the attempted rate, $f(AT)$ (the electronic time of use measure), $p<0.001$.

**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 three months (improvers) and those with a change <0.5 (non-improvers). In (a) the relationship between the changes in AQLQ and Average Adherence calculated from the Diskus™ dose counter is shown. Using this method of calculation of adherence, paradoxically, non-improvers had a higher level of adherence than those who improved. In (b) the relationship between the changes in AQLQ and Mean Daily Dose is shown. Non-improvers similarly showed no relationship between adherence and change in AQLQ. In (c) the relationship between the changes in AQLQ and Attempted Adherence is shown. Non-improvers 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. In (d)
the relationship between the changes in AQLQ and Actual Adherence is shown. Non-improvers 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 comparing Average Adherence (dose counter) with Actual Adherence and Average Adherence with Attempted Adherence, p<0.01 and p<0.03 respectively.

**Figure 5:** Twice daily Peak Flow (PEF) was divided into Morning (AM) and Evening (PM) readings. The mean variability between the AM and PM readings was calculated for each month for each patient. Figures (a)-(d) shows the change in AM-PM 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 AM-PM PEF Variability (slope of -0.8). There was a significant difference between Average Adherence with both \( f(AC) \) and \( f(AT') \), p=0.01 and p=0.03 respectively.
Table 1: The baseline characteristics of the study population reported is shown. Unless otherwise stated. For Forced Expiratory Volume in 1 second, Asthma Control Test at visit 1, Asthma Quality of Life Questionnaire at visit 1.

<table>
<thead>
<tr>
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<th>Mean±SD¹</th>
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<tbody>
<tr>
<td>NUMBER OF PATIENTS</td>
<td>239</td>
</tr>
<tr>
<td>AGE (YEARS)</td>
<td>49±16.1</td>
</tr>
<tr>
<td>NUMBER OF MALES (%)</td>
<td>91 (38%)</td>
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<tr>
<td>FEV1² L/SECOND</td>
<td>2.2±0.88</td>
</tr>
<tr>
<td>FEV1 (%) PREDICTED</td>
<td>74.1±22.9</td>
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<tr>
<td>NUMBER OF EXACERBATIONS IN THE PREVIOUS YEAR</td>
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<tr>
<td>ACT V1³</td>
<td>12.2±4.5</td>
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<tr>
<td>AQLQ V1⁴</td>
<td>3.9±1.3</td>
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<tr>
<td>NUMBER OF PATIENTS RELIEVER USE (%)</td>
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<tr>
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<tr>
<td>&lt;1/WEEK</td>
<td>15 (6%)</td>
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<td>8 (3%)</td>
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<tr>
<td>2-5/WEEK</td>
<td>22 (9%)</td>
</tr>
<tr>
<td>EVERY DAY</td>
<td>145 (61%)</td>
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</table>

¹Unless otherwise stated. ²Forced Expiratory Volume in 1 second. ³Asthma Control Test at visit 1. ⁴Asthma Quality of Life Questionnaire at visit 1.
Table 2: The mean adherence for all patients as calculated using different adherence measures. *The difference in the Average Adherence by dose counter and Attempted Adherence is due to multiple blisters and some unrecorded dose counters.

<table>
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<tr>
<td>Actual Adherence f (AC)</td>
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<td>Average Adherence from Dose Counter*</td>
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<tr>
<td>Mean Daily Dose</td>
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<tr>
<td>Attempted Adherence* f (AT)</td>
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<tr>
<td>Missed Dose Rate f (md)</td>
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<td>Over Dose Rate f (od)</td>
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<td>Technique Error Rate f (te)</td>
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</tbody>
</table>

Table 3: The number of patients considered adherent for various measures of adherence, using 80% as a cut-off for good and poor adherence. The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of the dose counter, Mean Daily Dose and Attempted Adherence in correctly classifying good and poor adherence relative to the Actual Adherence (using the traditional 80% cut-off for good adherence).

<table>
<thead>
<tr>
<th>ADHERENCE MEASURE</th>
<th>n</th>
<th>&gt; 80% Mean±SD</th>
<th>n</th>
<th>≤ 80% Mean±SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Actual Adherence f (AC)</td>
<td>67</td>
<td>90.9±4.5%</td>
<td>156</td>
<td>49.3±25.1%</td>
</tr>
<tr>
<td>Average Adherence from Dose Counter</td>
<td>153</td>
<td>93.4±12.0%</td>
<td>64</td>
<td>62.9±15.6%</td>
</tr>
<tr>
<td>Mean Daily Dose</td>
<td>161</td>
<td>94.2±14.0%</td>
<td>62</td>
<td>61.1±18.3%</td>
</tr>
<tr>
<td>Attempted Adherence f (AT)</td>
<td>140</td>
<td>91.4±5.4%</td>
<td>83</td>
<td>59.0±21.2%</td>
</tr>
</tbody>
</table>

ADHERENCE MEASURES COMPARED TO ACTUAL ADHERENCE

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average Adherence from Dose Counter</td>
<td>37.1%</td>
<td>93.0%</td>
<td>90.2%</td>
<td>46.2%</td>
</tr>
<tr>
<td>Mean Daily Dose</td>
<td>52.8%</td>
<td>96.6%</td>
<td>96.4%</td>
<td>54.1%</td>
</tr>
<tr>
<td>Attempted Adherence</td>
<td>43.0%</td>
<td>97.0%</td>
<td>96.2%</td>
<td>49.2%</td>
</tr>
</tbody>
</table>
Table 4: Adherence rates at month 3 and their relationship with changes in Asthma Quality of Life (AQLQ) and Peak Expiratory Flow (PEF). *≥10% improvement in AM PEF readings; **≥0.5 point improvement in AQLQ. Receiver Operator Curve (ROC) analysis demonstrates the sensitivity and specificity of each adherence measure in correlation to improvements in PEF and AQLQ.

<table>
<thead>
<tr>
<th>ADHERENCE MEASURE</th>
<th>PEF Improver*</th>
<th>PEF Non-Improver</th>
<th>AQLQ Improver**</th>
<th>AQLQ Non-Improver</th>
</tr>
</thead>
<tbody>
<tr>
<td>Actual Adherence (f(AC))</td>
<td>68.5±28.4%</td>
<td>65.7±27.6%</td>
<td>66.4±28.4%</td>
<td>64.4±27.3%</td>
</tr>
<tr>
<td>Average Adherence from Dose Counter</td>
<td>87.2±13.0%</td>
<td>89.4±14.5%</td>
<td>87.2±13.8%</td>
<td>88.6±15.3%</td>
</tr>
<tr>
<td>Mean Daily Dose</td>
<td>84.4±13.7%</td>
<td>84.0±16.3%</td>
<td>83.3±15.2%</td>
<td>83.6±16.5%</td>
</tr>
<tr>
<td>Attempted Adherence (f(AT))</td>
<td>81.8±16.6%</td>
<td>82.4±18.5%</td>
<td>82.1±16.5%</td>
<td>80.7±20.2%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Actual Adherence (f(AC))</td>
<td>59.8%</td>
<td>46.9%</td>
<td>66.7%</td>
<td>44.6%</td>
</tr>
<tr>
<td>Average Adherence from Dose Counter</td>
<td>19.5%</td>
<td>71.9%</td>
<td>19.2%</td>
<td>73.7%</td>
</tr>
<tr>
<td>Mean Daily Dose</td>
<td>27.1%</td>
<td>69.7%</td>
<td>25.0%</td>
<td>73.3%</td>
</tr>
<tr>
<td>Attempted Adherence (f(AT))</td>
<td>32.5%</td>
<td>63.6%</td>
<td>37.5%</td>
<td>66.0%</td>
</tr>
</tbody>
</table>
References


FIGURE 1: This is a photograph of the INCATM device attached to a salmeterol/fluticasone Diskus™ inhaler. The device contains a microphone, internal clock, a memory card and some circuitry. Every time the inhaler device is opened the INCATM starts recording audio of the patient using their inhaler with a date-time stamp.

Figure 1
127x135mm (150 x 150 DPI)
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(AT) is perfect, 60 doses taken over 30 days. There were no missed doses, no technique errors, and the interval between doses is within one half-life, the Actual Adherence rate, f(AC), is 1.00 (100%). Column B is an example where the medication was taken only once daily for 30 days. The Attempted Adherence, f(AT) is half that of column A and there were 30 missed doses over 30 days. In this example there were no technique errors. Due to missing doses every day the interval between doses was also poor and f(AC) is 0.50 (50%). Column C is an example of a patient who takes the medication (with no technique errors) every day, twice a day, but with erratic timing. There was perfect Attempted Adherence, with no missed doses and no technique errors. Due to the erratic time of use, some doses which have an interval beyond the half-life of the drug, f(i), the f(AC) is reduced to 0.92 (92%). Finally, column D is an example of a patient who takes the medication only once daily and makes a technique error for the first 15 days of the 30 days. Therefore, the, f(AT) is half that of expected (50%) due to missing 30 doses. There
were also 15 doses with technique errors, and due to missing doses every day the interval between doses was poor, therefore the f(AC) is 0.25 (25%).

Figure 2
254x338mm (300 x 300 DPI)
FIGURE 3: Graphical representation of adherence calculated in a number of ways. The data used for this graph is the first month’s inhaler use by a cohort of 217 (of 239) asthma patients enrolled in a prospective adherence intervention clinical study who were asked to use a dry powder inhaler twice daily. The Actual Adherence rate, $f(AC)$, is significantly different than the adherence calculated using the current methods, e.g. Average Adherence from the dose counter and the Mean Daily Dose, and the attempted rate, $f(AT)$ (the electronic time of use measure), $p<0.001$.
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 three months (improvers) and those with a change <0.5 (non-improvers). In (a) the relationship between the changes in AQLQ and Average Adherence calculated from the DiskusTM dose counter is shown. Using this method of calculation of adherence, paradoxically, non-improvers had a higher level of adherence than those who improved. In (b) the relationship between the changes in AQLQ and Mean Daily Dose is shown. Non-improvers similarly showed no relationship between adherence and change in AQLQ. In (c) the relationship between the changes in AQLQ and Attempted Adherence is shown. Non-improvers 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. In (d) the relationship between the changes in AQLQ and Actual Adherence is shown. Non-improvers 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 comparing Average Adherence (dose counter) with Actual Adherence and Average Adherence with Attempted Adherence, p<0.01 and p<0.03 respectively.

**Figure 4**

705x540mm (72 x 72 DPI)
FIGURE 5: Twice daily Peak Flow (PEF) was divided into Morning (AM) and Evening (PM) readings. The mean variability between the AM and PM readings was calculated for each month for each patient. Figures (a)-(d) shows the change in AM-PM 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 AM-PM PEF Variability (slope of -0.8). There was a significant differences between Average Adherence with both f(AC) and f(AT), p=0.01 and p=0.03 respectively.

Figure 5
705x540mm (72 x 72 DPI)