Title: A quantitative evaluation of adherence and inhalation technique among respiratory patients: an observational study using an electronic inhaler assessment device.

Running title: Novel technology for adherence assessment

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Abstract:

Background: Problems related to poor adherence and inhaler technique (IT) are historically reported in the literature. Most common methods used for adherence and IT assessment are reported to be either inaccurate or subjective. Few electronic monitoring devices (EMDs) that provide an objective measure of both adherence and IT while patients use inhalers at home now exist. Therefore, this study aimed to examine adherence level and IT among respiratory patients in community care using such an EMD for the first time in England.

Methods: A prospective, multicentre, observational cohort study was conducted. Patients with Chronic Obstructive Pulmonary Disease (COPD) or asthma were recruited from independent community pharmacies within West and South London. Patients were provided with a dry powder inhaler (DPI) mounted with an EMD to use for 1 month. Adherence was also assessed using pharmacy dispensing data, inhaler dose-counter and self-reporting.

Results: Data were available for 48 patients. Only 8 patients used their inhaler in the correct manner at the correct interval as identified by the chosen EMD. The median actual adherence rate, as measured by the EMD, was 42.7%. This was significantly different from the median dose-counter adherence (100%), medication refill adherence (100%), proportions of days covered (97.8%) and self-reported adherence ($p<0.001$, each). Within a one-month period, there were 2188 files showing attempted use of the DPI, of which 840 had IT errors. The median technique error rate was 30.1%. Most common errors recorded were: multiple inhalations, drug priming without inhalation and failure to prime the device correctly.

Conclusion: The current study demonstrates that measures such as dose-counter, prescription-refill and self-reporting showed a high level of adherence among the observed patients. However, the objective data provided by the EMD showed a significantly lower actual adherence rate, reflecting how adherence remains variable and problematic among patients in the community.

Key words: adherence, inhaler technique (IT), community pharmacy, electronic monitoring device (EMD), asthma, Chronic obstructive pulmonary disease (COPD).

What is already known about the topic?

- Problems of poor adherence and IT are historically reported in the literature among respiratory patients, with no signs of substantial improvement.
- Accurate assessment of adherence and IT is difficult in clinical practice, with traditional methods being reported either as inaccurate or subjective.

What does this article add?

- Using an EMD that assesses both adherence and IT, this study identified that the actual adherence among patients over a one-month period was as low as 42.7%.
- Only 17% of patients used their inhaler correctly and on time, echoing observations from patients in Ireland.
- Actual adherence was significantly lower compared to the currently established methods of adherence assessment such as dose-counter, self-reporting and prescription-refill, which calls into question the applicability of those methods.

1. Introduction

Over half of a billion people suffer from chronic respiratory conditions such as asthma or chronic obstructive pulmonary disease (COPD) [1,2]. The two conditions are considered as major public health challenges with substantial clinical, social and economic burdens worldwide [3-9]. Inhalation therapy is of paramount importance in the treatment of respiratory conditions [3,6,10-13]. However, problems related to poor adherence and inhaler technique (IT) among respiratory patients are widely and historically reported in the literature and still represent a challenge for healthcare professionals (HCPs) and healthcare systems to date [3,4,14-19]. Regarding IT, evidence in the literature suggests that 50-100% of patients perform errors while using their inhalers [18,20,21] . Furthermore, the literature suggests that deterioration in technique can occur as early as one month after receiving education about IT [22,23]. In terms of adherence, the evidence in the literature indicates that adherence rates among respiratory patients can widely vary ranging from 22%-78% and sometimes can be as low as 10-40% [8,24,25]. Poor adherence and IT are two aspects that significantly contribute to poor disease control leading to prescribing unnecessary higher doses, increased frequency of exacerbations and hospitalisation, high mortality, low quality of life and loss of productivity, hence increasing the clinical and economic burdens of these conditions [3-9]. For respiratory patients, some scholars argue for the incorrect use of inhalers to be a form of poor adherence or non-adherence [18,24,26]. Other scholars see that poor adherence can be triggered by the incorrect IT of the patient because of the latter's dissatisfaction with the medication response [9,10]. Whereas a third group of scholars [27-31] highlight that the notion of what is called true adherence incorporates two distinct components namely adherence and competence, with competence mainly being related to the patient's ability to use a medication in a correct and effective way which is also commonly referred to as technique. Hence, in case of inhaled medication, adherence and IT should be taken into consideration to reflect true adherence.

Unfortunately, there is no evidence in the literature for any substantial change/ improvement in the problem of incorrect IT over the past four decades [9,21,32-34], or the problem of adherence to medications used in the treatment of long-term conditions (LTCs) over the past five decades [35]. This is further escalated by the fact that the most common methods currently used for adherence and IT assessment are reported to be either inaccurate or subjective [15,29,36-38]. The use of electronic monitoring devices (EMDs), on the other hand, have been reported to provide a more accurate solution for monitoring IT and adherence to therapy for asthma and

COPD patients [39]. However, some of these EMDs assess adherence alone, whereas, others assess IT alone [38]. The inhaler compliance assessment device, commercially referred to under the trademark of INCA, is one of the few EMDs that has the advantage of being an automatic and objective measure of both adherence and IT while patients are using their inhalers at home [29, 37,40, 41]. The aforementioned device is a small acoustic, battery-operated device that is mounted on the top of a dry powder inhaler (DPI) (Figure 1). Once the inhaler is opened, the device becomes activated and starts recording the audio associated with inhaler use, in addition to the date and time and switches off once the DPI is closed [29,42] . Analysis of the recorded audio-files is conducted by an automated processing algorithm to provide quantitative information about the patients' technique, time and duration of inhaler use [30]. The device algorithm has an accuracy of 89%, sensitivity of 95% and specificity of 94% in detecting and determining inhaler technique steps related to inhalation, exhalation and drug priming [36]. The design and validation of the device has been previously published [29,36,38,42-45] . The device is certified (EU registered) [30] and has Food and Drug Administration (FDA) approval [22, 46] .

So far, studies involving the aforementioned device were only conducted in Ireland[30,47]. The Irish studies looked at assessing adherence and IT of asthma and COPD patients using the EMD. Interestingly, the Irish studies found that ineffective and irregular use is common among respiratory patients with only 20% of patients in the community[30] and 6% of patients after hospital discharge[47] using their inhaler correctly and on time. Therefore, the primary aim of this study was to examine the level of adherence and IT of COPD and asthma patients using this device for the first time in England. The secondary aims were to compare the abovementioned EMD as an adherence measure with established measures of adherence such as prescription-refill, the inhaler dose-counter and self-reporting. In addition, to identify and quantify the most common technique errors among asthma and COPD patients.

2. Methods:

2.1. Study design

The current study quantified over a one-month period how and when two cohorts of respiratory patients, asthma and COPD, recruited from several community pharmacies used a twice-daily preventer inhaler. Thus, this study was considered a prospective, multi-centre, observational

cohort study in a community care setting. Twenty-three independent community pharmacies based in South and West London participated in this study. A convenience sampling strategy based on local knowledge and proximity to the research team in England was employed for recruiting community pharmacies. A list of independent community pharmacies was identified through the National Health Service (NHS) choices website for pharmacies located within West and South London. Multiple chain pharmacies were excluded due to research governance requirements. Ethical approval for conducting this study was granted from the Research Ethics Committee at the academic institution of the corresponding author (Reference No. 1415/034). The study was initiated in October 2015 and was completed in June 2017.

2.2. Procedures

Patients were recruited from the participating community pharmacies. Inclusion criteria for patients were as follows: over 18 years old, diagnosed with asthma or COPD, using a combination long acting beta-agonist/inhaled corticosteroid inhaler: salmeterol/fluticasone DPI for at least 6 months, regular customers of the participating pharmacies, capable of understanding and willing to provide voluntary informed consent. Patients were excluded if they were under 18 years of age, illiterate or with language barrier, not using salmeterol/fluticasone DPI, mentally incapacitated, or involved in another study at time of recruitment. Patients were recruited by community pharmacists, hence inclusion and exclusion criteria were provided by the research team to the participating pharmacists in order to guide the recruitment process. Written informed consent was obtained from each patient by the corresponding community pharmacist prior to study start.

Once informed consent was obtained from patients, the chosen EMD was mounted on the top of their DPI. Patients were asked to use the mounted DPI as usual and return it to the pharmacy when they finish it (i.e.: after one month). No training about IT was provided to the patients because the main aim of the study was to assess the patients' level of adherence and IT in a real-world setting. Demographic data on age, gender, educational level, marital status, socioeconomic class, clinical diagnosis, healthcare utilisation and self-reported adherence were obtained from participants. Furthermore, patients' medication refill data for the salmeterol/fluticasone DPI was retrospectively obtained for the last 6 months prior study start from community pharmacies.

2.3. Outcome measures

Adherence to maintenance therapy (salmeterol/fluticasone DPI)

Objective adherence: the adherence rate for each patient measured using the chosen EMD was calculated as an area under the curve (AUC) metric. This method of adherence calculation was previously described in details by Sulaiman et al [31]. Initially, the AUC was calculated for the patient's "attempted adherence". Afterwards, the AUC was calculated for the patient's "actual adherence", which denotes attempted adherence at the correct intervals with no technique errors [47,48].

Dose counter adherence: this was calculated by dividing the number of doses used according to the dose counter by the total expected doses to be taken monthly, which is 60, multiplied by 100.

Prescription refill adherence: This was assessed retrospectively using medication refill adherence (MRA) [49] and proportions of days covered (PDC) [50] for a six-month period prior study start for the salmeterol/fluticasone DPI.

Self-reported adherence: the modified version of inhaler adherence scale (IAS) was used[51-53]. The scale consists of four questions with five-point Likert scale responses, with 1 indicating "Most of the time" and 5 indicating "None of the time" for the frequency of forgetting or stopping the use of the maintenance inhaler. Higher scores reflect better adherence to inhalation therapy[53,54]. The IAS score was calculated from the mean responses to the four questions. Thus, the mean IAS score can range from 1 to 5, with 5 indicating optimal adherence. The modified scale has good psychometric properties (Cronbach α =0.86) [53].

Based on the literature [4,49,55-57], the cut-off point for a patient to be considered as adherent is having a value of ≥ 80% for the dose counter, MRA, PDC and the EMD adherence measures. As for self-reported adherence, an overall IAS score of ≥4 was considered as having good adherence, whereas a mean score of <4 was considered as having some level of poor adherence [54].

Inhaler technique

IT was assessed objectively and quantitatively for one month using the chosen EMD. The technique error rate (TER) for a one-month period was calculated by dividing the number of files with technique errors by the total number of files when the inhaler was used, multiplied by 100. According to literature, a cut-off point of ≥80% is widely used to indicate good

adherence [4,49,55-57], and since IT is a form of non-adherence [18,24,26]; therefore, a TER of >20% was considered as a form of poor IT in the current study.

2.4. Statistical analysis

Descriptive statistics were performed to describe characteristics of patients and errors in inhaler use. Mean and standard deviation (SD) were used to describe continuous variables with normal distribution. Continuous variables that were not normally distributed were expressed using median and range. Proportions/percentages were used to describe categorical variables. In addition, frequencies were used to describe the distribution of different inhaler errors. The normality of data distribution was tested using Shapiro Wilk test [58]. Continuous/scale variables with normal distribution were compared using t-tests; whereas for variables that were not normally distributed, this was performed using Wilcoxon signed-rank test.

Correlations between data were analysed using Kendall tau-b rank correlation coefficient (denoted by τ_b) for non-normally distributed data. Furthermore, adherence variables were classified as binary based on the adherence level into good adherence and poor adherence. Good adherence level was based on a cut-off point of ≥ 80% for adherence measures via the EMD, dose counter, PDC and MRA and a cut-off point of ≥ 4 for the IAS self-reported adherence, and poor level otherwise [4,49,54-57]. These binary variables were then correlated using Phi correlation coefficient (denoted by $r\varphi$).

Analysis was performed using SPSS for Windows version 23. The level of statistical significance was set at $p<0.05$ for all analyses.

3. Results:

3.1. Study population and demographics:

Fifty-five patients were recruited over the study period and provided with a DPI mounted with the EMD. Four patients (7.2%) did not return the mounted DPI, one patient (1.8%) withdrew from the study, and two EMDs (3.6%) were not functional. Therefore, 48 patients with usable information were included in the study. The median age of participants was 65 years, with 60% (n=29) diagnosed with COPD and 40% (n=19) diagnosed with asthma. Demographic characteristics for patients with acoustic data are presented in table 1.

3.2. Adherence level among COPD and asthma patients using the designated EMD

Acoustic recordings were available for 48 patients; 2880 doses were expected to be taken in a one-month period (48*60 =2880 doses). The total number of doses taken according to the dose counter for the 48 patients was 2843, however there were 2601 audio files of attempted use by the EMD. This difference was attributed to errors related to drug priming.

Although patients were instructed to return their DPI after one month, many patients used their DPI beyond the ideal 30 days period. Therefore, audio files beyond one-month period were excluded from the analysis. Adjusting for one-month usage, there were 2188 audio files recorded with attempted use and 1348 audio files with correct technique (i.e.: actual doses). Of 60 doses expected to be taken monthly per patient, a median of 51 (85%) doses were attempted and when technique errors were accounted for, the median number of actual doses was 30 (50%).

Most patients used their DPI irregularly, in contrast to the twice per day, twelve hours apart regime, as there were periods of excessive dosing (≥ 3 doses in 24 hours) and periods of missed doses (<2 doses in 24 hours), accounting for 118 extra doses and 510 missed doses within one-month period. In fact, more than two-third of patients (69%, n=33) had periods of excessive dosing and 92% (n=44) had periods of missed dosing. Only 8% of patients (n=4) did not have any periods of missed dosing and excessive dosing during the one-month period.

The median attempted adherence using the EMD was 72.7% (range: 15.9-100) (Table 2). Notably, 40% of patients had attempted adherence rate between 80-100%, followed by one-third of patients (33%) having attempted adherence rate between 60-79%, 10.5% with adherence rates between 40-59%, 12.5% had attempted adherence rate between 20-39%, and only 2 patients (4%) had very low attempted adherence rate between 0-19% (Table 3).With a cut-off point of 80% for good adherence, 40% of patients had an attempted adherence ≥ 80% and 60% had a rate <80% (Table 4).When the interval between doses and technique errors were included in the adherence calculation, the median actual adherence using the EMD was 42.7% (range: 0-96.4) (Table 2). Interestingly, nearly one third of patients (31%) had very low actual adherence rate (0%-19%), 14.5% had adherence rate between 20-39% and 40-59% equally, 23% had actual adherence rate between 60-79% with only 17% having actual adherence rate between 80-100% (Table 5). Based on a cut-off point of 80% for good adherence , only 8 patients (17%) out of 48 used their inhaler in the correct manner at the correct interval, i.e.: had

an actual adherence ≥80%, whereas the majority (83%) had an actual adherence rate <80% (Table 4). Significant difference was observed between attempted adherence and actual adherence (p<0.001). Although COPD patients had higher attempted adherence compared to asthma patients, yet statistical analysis did not reveal any significant difference (p=0.089). Furthermore, there was no significant difference in the actual adherence rate between asthma and COPD patients (p=0.649).

3.3. Comparison of adherence from the designated EMD with the other established adherence measures

The median number of doses taken from dose counter was 60 doses and the median adherence rate using this method was 100% (range: 76.7-100) (Table 2). Dose-counter adherence rate was significantly different from the attempted adherence rate (p<0.001) and the actual adherence rate (p<0.001) obtained via the EMD. According to this method for assessing adherence, only one patient (2%) had an adherence rate <80% (Table 4), whereas 40 patients (83%) had an actual adherence rate <80% as measured by the EMD. No significant associations were found between dose-counter adherence with attempted adherence ($r\varphi$ =.118, p=0.413) or actual adherence ($r\varphi$ =.065, p=0.651) as measured by the EMD.

The median MRA was 100% (range: 33.3-133.3). MRA was significantly different from both attempted and actual adherence rates (p<0.001, each) as measured by the EMD. When using MRA for assessing adherence, 19% of patients had a MRA<80% and 81% had an adherence rate ≥ 80% (Table 4). Thus, there were 39 patients with MRA≥ 80% as opposed to only 8 patients having an actual adherence ≥80% as indicated by the EMD. No significant associations were found between MRA with attempted adherence ($r\varphi$ =.061, p=0.671) or actual adherence ($r\varphi$ =.215, p=0.137) as measured by the EMD.

The median PDC was 97.8% (range: 33.3-100). PDC adherence rate was significantly different from attempted adherence rate (p<0.001) and actual adherence rate (p<0.001) as measured by the EMD. When using PDC for assessing adherence, 77% of patients (n=37) were found to have an adherence rate ≥ 80%, and 23% had a PDC<80% (Table 4), compared to 17% (n=8) having an actual adherence ≥80% as measured by the EMD No significant associations were found between PDC with attempted adherence ($r\varphi$ =.137, p=0.342) or actual adherence ($r\varphi$ =.244, p=0.091) as indicated by the EMD.

As for self-reported adherence, the overall mean IAS score was 4.43 (95% CI: 4.2-4.6) (Table 2). Nearly half of the patients (n=23/48, 48%) had an overall mean score of 5 indicating optimal adherence. Based on a cut-off point of 4 for good adherence [53], 39 patients (81%) were classified as having good adherence and 9 (19%) showed some level of poor adherence. There was a significant difference between patients' self-reported adherence and each of attempted and actual adherence rates ($p<0.001$) obtained via the EMD. Interestingly, a significant positive association was observed between self-reported adherence and attempted adherence ($r\varphi$ =0.389, p=0.007) as measured by the EMD, but not with actual adherence ($r\varphi$ =.215, p=0.137). A possible explanation for that would be the fact that calculating actual adherence via the EMD takes into account errors in IT and interval between doses, which are not perceived by patients as a form of non-adherence. However, attempted adherence as generated by the EMD does not take into account technique errors or dose interval.

3.4. Inhaler technique among COPD and asthma patients using the designated EMD

The median TER per patient was 30.1% (range: 0-100) (Table 6) indicating an overall poor level of IT among the observed patients, based on a cut-off point of 20%. Analysis of the audio data showed that 1348 files (62%, n=1348/2188) followed the correct technique of inhaler use and 840 (38%, n=840/2188) had errors in the technique in a one-month period. Errors in drug priming which is the first step in inhaler use accounted for 17.4% (n=146/840) of all errors (Table 7). There were 26 audio files (3.2%) with evidence of more than one drug blister with/without inhalation which suggests dose wasting. Errors in inhalation accounted for 82.6% (n=694/840) of all errors. Multiple inhalations was the most prevalent error as it was recorded in 49.5% (n= 416/840) of all events, followed by drug priming without subsequent inhalation which accounted for 29.5% of all errors and lastly failure to prime the inhaler correctly which was recognised in 120 events (Table 7). The mean number of errors per patient in a one month's period was 11 (95% CI: 8-16) (Table 6). Besides, there was a trend of persistent technique error among some patients; for example, eight patients performed multiple inhalations more than 20 times in a one-month period, seven patients had the error "blister present but no inhalation detected" more than 15 times and three patients had the error "no blister detected but inhalation present" more than 18 times, during the one-month observation period.

There was no significant difference in TER between COPD and asthma patients (p=0.67). The comparison between both cohorts revealed that COPD patients audio records showed

more errors than those of asthma patients in a one-month period but this was not statistically significant (p=0.54) (Table 6).

Based on a cut-off point of 20% for IT, 60% of patients (n=29/48) were found to have a high TER within a one-month usage of their DPI compared to 40% (n=19) who demonstrated a low TER. Only 2 patients (4%) did not commit any error during the one-month period, whereas the rest of patients (96%, n=46/48) committed errors during the one-month observation period. There was a strong negative association between actual adherence as measured by the EMD with TER (τ_b = -.702, p<0.001).

4. Discussion:

The current research provided an insight into the adherence level and technique rate and errors among asthma and COPD patients in community care in England using a quantifiable measure used in patient's home. Analysis of the audio recordings from the chosen EMD showed that most patients made errors in both inhaler use and technique. In the current study, the data generated from the EMD provided an actual adherence rate of 42.7% when incorporating technique and interval between doses, with only eight patients (17%) out of the 48 having an actual adherence of ≥80%. This is comparable to the observational study conducted in Ireland among 103 asthma and COPD patients from primary care and community pharmacies (large multiple chain: Boots Pharmacy Inc.) using the same EMD [30]. In the latter study, patients had a mean actual adherence of 47%, thus highlighting how ineffective and irregular inhaler use can be a common problem. The study showed that only 20% of patients were using their inhalers correctly and on time, i.e.: having an actual adherence ≥80%. This highlights that the current findings from independent community pharmacies echo findings from multiple chain pharmacies in Ireland. Interestingly, another observational study [47] using the same EMD among 179 COPD patients recruited upon hospital discharge in Ireland showed an even lower mean actual adherence of 22.6%, with only 6% of patients having an actual adherence ≥80%.

Different methods have been employed to assess adherence in the literature. However, most studies were found to employ a mixture of subjective and objective methods, mainly a self-reporting scale as a subjective method in conjunction with prescription refill adherence as an

objective method [4,18]. However, it can be argued against the latter method being considered objective, given the findings of the current study and the fact that prescription refill adherence does not assess actual medication-taking behaviour [41,59]. Comparisons between the different adherence measures in the current research revealed that in real-life situations, commonly used adherence measures such as dose-counter, self-reporting and prescription refill data are not accurate in reflecting the actual adherence behaviour of patients since these measures were significantly higher than the actual adherence rate as measured by the designated EMD. This is due to the fact that the chosen EMD provides objective information on both the point in time (temporal adherence- which provides an indication about intentional non-adherence) and the user technique (technique adherence, which may be considered as unintentional non-adherence) each time the patient uses the inhaler [30,47]. Hence, when both aspects are combined in the adherence calculations, a significantly lower actual adherence rate is calculated compared to established measures of adherence [30]. This discordance in results between the actual adherence as measured by the EMD and the other established adherence measures was similarly reported by studies conducted in Ireland using the same EMD [30,47,48] . This in return calls into question the previously established adherence measures that are used in research (prescription refill, dose counter and self-reporting) and their applicability in real-life situations. Given the generated results, the use of the designated EMD would be useful in clinical practice particularly for respiratory patients, who despite therapy optimisation, still show no improvement in their condition or still have their condition uncontrolled. HCPs do not usually know how a patient is using their inhaler once they take the inhaler home with them. Thus, the use of the designated EMD will help and guide HCPs to better identify and distinguish whether the progression of condition is influenced by adherence to therapy or deterioration in the condition.

A previous research in Ireland, which aimed to compare the same EMD against established adherence measures, highlighted the absence of associations between actual adherence with prescription refill (using PDC and medication possession ratio) and self-reported adherence [48], but a small association between attempted adherence with prescription refill. The same Irish study also revealed significant correlations between adherence rates measured via the EMD with adherence from dose counter [48]. In the current research, the attempted adherence was significantly associated with self-reported adherence but not with prescription refill, with no association between actual adherence and all other adherence measures. The association seen with self-reported adherence might be due to the fact that the self-reporting measure used in

the current research was specific to inhalers unlike the one used in the Irish study which examined adherence more generally and this was noted in the Irish study. The correlation between dose counter and adherence measures via the EMD in the Irish study can be attributed to the fact that participants were provided with the DPI by the research team and hence the DPIs were collected via a courier between 28-30 days following recruitment, hence adherence rate from dose counter was reflective of the one-month usage. Whereas in the current research, provision of the DPIs by the research team was not feasible, this resulted in extended usage of the DPI beyond the one-month period due to missing doses especially among poor adherers, although patients were instructed to return the DPI after a one-month period upon recruitment, hence the obtained adherence rate from dose counter was not reflective of the one-month usage across all patients.

An interesting and important feature of the chosen EMD is the ability to identify the type of technique errors and quantify the frequency of these errors at the same time [30]. The most common technique errors identified in the current research were multiple inhalations, drug priming present with no subsequent inhalation followed by failure to prime the inhaler correctly which occurred in 14.2% of all inhalations. However, in the two observational studies done by Sulaiman et al. [30,47] using the same EMD; one among 179 COPD patients upon hospital discharge [47] and the other among 103 asthma and COPD patients from primary care and community pharmacies [30]; the most common errors identified were low peak inspiratory flow rate (<35 L/min), multiple inhalations followed by presence of drug priming with no subsequent inhalation. With respect to other studies which used the checklist method as a way to assess IT, a recent large systematic review over the past 40 years showed that the most common errors with DPIs were: no full exhalation before inhalation (46%), insufficient breath hold (37%) and incorrect preparation including loading the dose (29%) [32]. This disparity can be attributed to the difference in the nature of the methods used to assess technique errors between the current study and the literature that use the checklist method for assessing IT.

The aforementioned systematic review [32] also concluded that there has been an unacceptable high frequency of incorrect inhaler use over the past 40 years, while highlighting the necessity to identify new and better approaches to tackle this problem besides the already recommended strategies such as careful instruction, observation of IT, and individual matching of inhaler to meet patients' needs and preferences [32].The review [32] based on studies which utilised the checklist method for assessing IT, concluded that the mean percentage of poor IT when using DPIs over the past 40 years was 23% [32]. For studies utilising the checklist method, another

systematic review also estimated an overall error frequency of 60.9% of patients using DPIs committing at least one error, while noting a high level of heterogeneity between the reviewed studies [20]. However, in the current study, 60% of patients (n=29/48) had a high TER (TER>20%) and the median TER was 30.1% for a one-month period usage among patients at home, as indicated by the EMD. In addition, only two (4%) patients did not commit any error during the one-month observation period.

The mean number of errors per patient in the current study was 11, which indicates that even in the case of ideal adherence to twice-daily inhaled therapy (i.e. without missing any single dose); patients tend to get reduced amount or no drug in 11 uses out of 60 per month. Comparing to the two observational studies conducted by Sulaiman et al. [30,47] ; the mean number of errors per patient among 179 COPD patients discharged from hospital was 20 [47], which is higher than the current findings. Whereas, the mean number of errors per patient among 103 COPD and asthma patients recruited from primary care and community pharmacies was 12 [30], which is similar to the current findings. Another remarkable observation in the current research was that some patients exhibited a pattern of persistent technique error of the same type; this was identified through quantifying errors for each patient. This in return highlights the potential of technological developments such as the designated EMD in identifying technique errors outside clinical environments to assist in a problem, which does not seem to have improved over the last 4 decades [32]. Education about IT should not be considered as a perfunctory practice, which means that HCPs are required to pay more attention to the quality of this education by making it clear, short in content and focused[60]. Thus, EMDs, such as the one used in this study, can facilitate the provision of individually tailored and focused interventions through discussing the personalised feedback provided by the device, which can elicit technique errors. According to social cognitive theory, performance mastery experience (i.e. doing something correctly) is one of the tactics to promote self-efficacy [22]. Hence, if patients are made aware of the specific inhaler steps they do incorrectly using the feedback generated from the device, then they can rectify these errors, which in return could foster their confidence to use their inhalers in a correct manner [22].

4.1. Strengths and limitations

The current research has several strengths. This is the first study conducted in England using the designated EMD as a quantifiable measure of adherence outside clinical environment. Second, this was the first study to objectively quantify inhaler technique errors to preventer

inhaled therapy among patients in the community care setting in England. However, the results should be considered within the context of several limitations including; first the small sample size. Second, possibility of selection bias for community pharmacists and patients cannot be excluded since participation in research studies usually involves motivated people. Third, recruitment was limited across independent community pharmacies within South and West London. Fourth, recruitment was limited to patients using only salmeterol/fluticasone DPI, which limits the generalisability of the results. Fifth, patients were recruited based on self-reported general practitioner (GP)-diagnosis about asthma or COPD, with confirmation being acquired from the community pharmacists but not from the patients' GPs.

5. Conclusion

The current study demonstrates that while measures such as dose counter, prescription refill and self-reporting showed a high level of adherence among the observed patients, yet the objective data provided by the EMD showed a significantly lower actual adherence rate, reflecting how adherence remains very variable and problematic among patients in the community. The objective data showed that only 8 patients out of 48 used their inhalers correctly and on time.

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Tables:

Characteristics	All (N=48)	Asthma (n=19)	COPD (n=29)
Age (y), median (range)	65 (22-82)	65 (22-81)	65 (46-82)
Female patients, n (%)	24 (50)	9 (47)	15 (52)
Male patients, n (%)	24 (50)	10 (53)	14 (48)
Smoking history, n (%)			
Non-smoker	16 (33)	11 (58)	5 (17)
Current smoker	10 (21)	0 (0)	10 (35)
Ex-smoker	22 (46)	8 (42)	14 (48)

Education Level, n (%)			
Primary	1(2)	0 (0)	1 (3)
Secondary	22 (46)	7 (37)	15 (52)
College	12 (25)	5 (26)	7 (24)
Undergraduate	4 (8)	2 (11)	2 (7)
Postgraduate	9(19)	5 (26)	4 (14)
Marital status, n (%)			
Single	10 (21)	4 (21)	6 (21)
Married	25 (52)	12 (63)	13 (45)
Divorced	5 (10)	1 (5)	4 (14)
Widow/Widower	8 (17)	2 (11)	6 (21)
Residential area, n (%)			
Kingston Upon Thames	6 (12)	3 (15.7)	3 (10)
Richmond Upon Thames	20 (42)	10 (53)	10 (35)
Wandsworth	1(2)	0 (0)	1(3)
Merton	14 (29)	3 (15.7)	11(38)
Sutton	7 (15)	3 (15.7)	4 (14)
Flu vaccination, n (%)			
Yes	37 (77)	13 (68)	24 (83)
No	11 (23)	6 (32)	5 (17)
Pneumococcal vaccination, n (%)			
Yes	25 (52)	8 (42)	17 (59)
No	23 (48)	11 (58)	12 (41)
Presence of comorbidities, n (%)			
Yes	34 (71)	12 (63)	22 (76)
No	14 (29)	7(37)	7(24)
No. of comorbid conditions, median (range)	2 (1-5)	1 (1-3)	2 (1-5)
No. of medications, median (range)	8 (2-16)	4 (2-16)	10(2-16)
No. of GP visits per year, median (range)	2 (1-6)	2 (1-6)	2 (1-6)
Exacerbations during the last year, n (%)			
Yes	22 (46)	5 (26)	17 (59)
No	26 (54)	14 (74)	12 (41)
No. of exacerbations during the last year, median (range)	3 (1-8)	3 (1-5)	3(1-8)
A & E visits during the last year, n (%)			
Yes	6 (12.5)	1(5)	5 (17)
No	42 (87.5)	18 (95)	24 (83)
No. of A & E visits during the last year, median (range)	2 (1-4)	4 (4)	2 (1-3)
Hospital admissions during the last year, n (%)			
Yes	6 (12.5)	1 (5)	5 (17)
No	42 (87.5)	18 (95)	24 (83)
No. of hospital admissions during the last year, median (range)	1 (1-3)	1 (1)	1 (1-3)

Table (1): Demographic characteristics for patients with available acoustic data.

Adherence measures	All	Asthma	COPD
Percentage attempted adherence as measured by the EMD, median (range)	72.7 (15.9-100)	68 (15.9-98.2)	78.8 (17.1-100)
Percentage actual adherence as measured by the EMD, median (range)	42.7 (0-96.4)	42 (0-96)	48.4 (0-93)
Mean IAS score, mean (95%CI)	4.43 (4.2-4.6)	4.27 (3.87- 4.7)	4.54 (4.2-4.7)
Percentage MRA, median (range)	100** (33.3-133.3)	100 (33.3-116.7)	100 (50-133.3)
Percentage PDC, median (range)	97.8** (33.3-100)	90.6 (33.3-100)	97.8 (46.1-100)
Percentage adherence rate from dose counter, median (range)	100** (76.7-100)	100 (95-100)	100 (76.7-100)

Table (2): Breakdown of different measures of adherence.
Abbreviations:CI, Confidence Interval; IAS, Inhaler Adherence Scale; MRA, Medication Refill Adherence; PDC, Proportions of Days Covered.
** Indicate statistical significant difference compared to attempted adherence and actual adherence as measured by the EMD at $p<0.01$.

	Attempted adherence rate as measured by the designated EMD (%)	Number of patients (N=48)	COPD (n=29)	Asthma (n=19)
Adherence rate <80%	0%-19%	2 (4%)	1	1
	20%-39%	6 (12.5%)	2	4
	40-59%	5 (10.5%)	2	3
	60-79%	16 (33%)	11	5
Adherence rate ≥80%	80-100%	19 (40%)	13	6

Table (3): Attempted adherence range by 20% bands and the frequency of patients within each band.

Adherence measure	Patients having ≥80% adherence, n (%)	Patients having <80% adherence, n (%)
Adherence as measured by the designated EMD		
Attempted adherence	19 (40)	29 (60)
Actual adherence	8 (17)	40 (83)
Dose counter adherence	47 (98)	1 (2)
MRA	39 (81)	9 (19)
PDC	37 (77)	11 (23)

Table (4): Frequency and percentage of patients' adherence according to the different measures of adherence based on a cut-off point of 80%.

	Actual adherence rate as measured by the designated EMD	Number of patients (N=48, %)	COPD (n=29)	Asthma (n=19)
Adherence rate <80%	0%-19%	15 (31%)	9	6
	20%-39%	7 (14.5%)	4	3
	40-59%	7 (14.5%)	5	2
	60-79%	11(23%)	6	5
Adherence rate ≥80%	80-100%	8 (17%)	5	3

Table (5): Actual adherence range by 20% bands and the frequency of patients within each band.

	All	Asthma	COPD
TER (%) per patient, median (range)	30.1 (0-100)	34 (0-100)	27.5 (0-100)
IT errors per patient, mean (95% CI)	11 (8-16)	10 (6-17)	12 (8-19)

Table (6): IT errors and TER as measured by the designated EMD.
Abbreviation: CI: Confidence Interval; IT, Inhaler Technique; TER, Technique Error Rate.

Audio error	Number of audio files (n=840)	Percentage
Errors in drug priming /drug blistering		
No drug priming , inhalation detected (failure to prime the device correctly)	120	14.2
Multiple drug priming	16	2
Multiple drug priming and multiple inhalation	10	1.2
Dose dumping	0	0
Total	**146**	**17.4**
Errors in inhalation		
Exhales into the inhaler after drug priming and before inhalation	30	3.6
Drug priming present, no subsequent inhalation detected	248	29.5
Multiple inhalations	416	49.5
Total	**694**	**82.6**

Table (7): The type of different inhalation errors observed.

Figure legends:

Figure (1): The inhaler compliance assessment device attached to a dry powder inhaler. Permission to reproduce the figure of the inhaler compliance assessment device was granted from Vitalograph Ltd [40].

Authors contributions

All authors contributed to the design of the study. Iman Hesso drafted the manuscript. Reem Kayyali and Shereen Nabhani Gebara helped to draft the manuscript and contributed towards the critical revision on all versions of the manuscript. Iman Hesso conducted the study (recruitment and data collection). Iman Hesso, Shereen Nabhani Gebara, Garrett Greene, R W Costello and Reem Kayyali contributed to data management, data analysis and checking of the final results. All authors read and approved the final manuscript.

Funding

This was a researcher-initiated study funded by the academic institution of the corresponding author. The research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Disclosure Statement

The author R W Costello is named on a patent for the INCA™ device. However, the main aim of this research was to examine the level of adherence and inhaler technique of COPD and asthma patients using the INCA™ device for the first time in England. All other authors have no conflict of interest to disclose and are not listed on the patent.