Electronic Monitoring of Adherence to Inhaled Medication in Asthma

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Abstract: The main treatment of asthma is inhaled corticosteroids. However adherence to these medications in asthma is often poor, with low adherence associated with excessive health care costs and an increased risk of emergency room visits and mortality. Although various methods are used to indirectly assess adherence, all have significant limitations whether used in clinical or research practice. The recent development of electronic monitoring devices (EMDs) for use with inhalers presents an exciting opportunity to easily and accurately measure inhaler adherence. This article summarises the current devices available; for each device features and limitations are considered, followed by a review of both the current clinical literature and data on reliability and accuracy. An overall summary is also provided to aid comparison of capabilities between devices and future issues pertaining to the use of EMDs are discussed, including barriers to adoption, stakeholder involvement, novel methods of communicating adherence data, recording of data and cloud storage. Finally key areas that still require investigation are highlighted.

Keywords: Asthma, adherence, electronic monitoring, inhaled medication, data

INTRODUCTION

Cost of Asthma

Asthma is a chronic respiratory condition with symptoms including wheezing, dyspnoea and cough. A patient is diagnosed with asthma based on the presence of such symptoms together with evidence of variable airflow obstruction or airway inflammation [1]. The U.K. has one of the highest prevalence rates in the world with around 6% of the general population diagnosed with asthma [2]. Similarly, in the U.S.A, statistics from 2009 indicate that asthma prevalence stands at 8.2%, equivalent to roughly 24.6 million people, accounting for 10.5 million missed school days and 14.2 million sick days at work [3].

The direct costs associated with asthma present a significant burden on society and healthcare systems. In the UK current estimates highlight an annual care cost of around £1 billion [2]. Furthermore it is estimated that the total incremental cost of asthma to society in the USA is $56 billion [4]. This is despite asthma being a highly treatable condition with effective medication available to reduce symptoms and prevent asthma attacks [5].

The Problem of Non-Adherence in Asthma

It is easily arguable that poor adherence is the most pressing issue in the proper management of asthma. There is robust evidence that adherence to asthma treatment is variable and often poor. Rates of non-adherence tend to range from 30% to 70% [6], whereas for optimum control of asthma, and thus minimum healthcare costs, a patient is normally required to adhere to 80% or more of their prescribed medication [7].

A study over 30 years of 30,569 people with asthma aged from 5 to 44 years found a significant correlation between increased use of inhaled corticosteroids (ICS) and a decreased risk of death from asthma [8]. Similarly, a study over 7 years with 12,301 children and adults with asthma aged 5-54 found a significant positive correlation between overuse of short-acting beta agonists (SABA) and asthma mortality [9]. This clearly highlights the importance of adhering to prescribed treatment for asthma. If a patient

properly uses ICS, research suggests there is a reduced risk of death from their asthma. However, if a patient does not adhere to their ICS and instead relies on their SABA to relieve severe symptoms, they may be at an increased risk of death.

The risks of non-adherence have made measuring and investigating ways of improving adherence a priority for researchers and clinicians alike [10].

Methods of Measuring Adherence in Asthma

Various methods have been used to monitor adherence in asthma, the simplest of these being to directly ask the patient how adherent they have been. Whilst self reported measures can be a useful and intuitive method of receiving feedback on a medical regime [11], it has been shown to be unreliable, with patients estimating their adherence as 80% compared to a true adherence rate of 50% [12]; in some cases full adherence is reported, when adherence is actually 0% [13].

Canister weighing has been extensively used as a method of measuring adherence. Here, the weight of an inhaler canister at the point of prescription is compared with the weight of the same inhaler canister when it is returned by the patient in order to calculate an adherence score [14]. Whilst this is relatively simple and easy to implement, canister weighing has a number of major pitfalls, the most significant being an inability to provide precise data on patterns of inhaler use, meaning exact information on a patient's asthma treatment cannot be obtained. As a result of this imprecision, canister weighing is also unable to detect 'dose dumping' [15], when a patient deliberately actuates their inhaler multiple times consecutively over a short period of time in order to give the appearance of optimal adherence to the clinician or researcher [14].

Pharmacy database records have been used as a source of information on adherence, providing data on type of medication, amount prescribed, and refills. However, there are similar issues to canister weighing with a low level of data granularity meaning the total number of administered doses is estimated over weeks or months, rather than hours or minutes [14] and 'dose dumping' remains undetectable. Research has shown pharmacy records to be less accurate than both electronic monitoring and canister weighing [16].

Another way to detect non-adherence is through use of fractional exhaled nitric oxide (F_ENO) [17]. Through directly observed inhaled steroid therapy over seven days adherent patients can show a greater reduction in F_ENO . This method can serve as an objective test to distinguish between difficult asthma and asthma in patients who are non-adherent to their ICS therapy, who may fill in prescriptions yet fail to take their medication [17].

Although barriers currently exist to their widespread use, electronic monitoring probably offers the most accurate practical measure, and the measure by which other methods should be compared [12,18,19]. Although devices for other types of inhaler exist, it was decided that this article would focus on devices for standard metered dose inhalers (MDI) as this is where the majority of research and development has occurred.

ELECTRONIC MONITORING DEVICES (EMD)

For the purposes of this article EMDs will refer to devices for monitoring use of MDIs, it will not refer to other devices for use in asthma treatment such as electronic spirometers. The devices described below all have at least one feature in common; they record actuations of an MDI. Specific criteria such as their ability to record the date and time of dose, battery life, memory capacity, and a visual display for feedback of last dose taken or doses taken over time are also discussed. Where literature and data are available, important information on how accurately the device can keep a record of actuations, a percentage of devices that fail, and use of the device in a clinical trial are also mentioned.

Nebulizer Chronolog
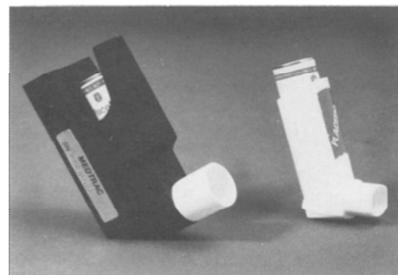
Fig.(1). A Nebulizer Chronolog (left) alongside an inhaler (right) in its usual plastic holder that the Nebulizer Chronolog replaces [20] (image included with permission from BMJ Publishing Group Ltd.).

The Nebulizer Chronolog (NC) (Fig.**1**.) was developed by Forefront Engineering Corp, Denver, Colorado, USA [21] and was the first device to gain FDA (Food and Drug Administration) approval as a monitoring device for asthma [22]. The NC replaces the usual plastic casing surrounding the inhaler canister, allowing for the canister to be used within the NC's own casing and mouthpiece [20].

The NC records actuations of the inhaler through a micro-switch that is activated every time the inhaler is used. The date and time of each actuation are recorded, with the ability to store roughly 4,000 actuations in the devices memory [21]. Data can then be uploaded to a Personal Computer (PC) for analysis [19].

Features

- Records date and time of actuations
- It can be used with any aerosol inhaler canister [20]

- Data from the NC can be uploaded to a PC
- Food Drug Administration (FDA) approved [22]

Limitations

- Only compatible with a press-and-breathe metered dose inhaler (MDI), not compatible with a breath activated inhaler [21]
- Not compatible with spacers
- Does not detect inhalation
- Does not detect shaking of inhaler
- Does not record data on technique nor provide feedback to patient on this
- No feedback screen, data can be only be viewed once uploaded to a PC.
- Increases the size of the inhaler

Relevant Literature

The NC was utilised in a three-month pilot study investigating adherence in fourteen children with asthma on prophylactic treatment [20]. The NC demonstrated underuse of medication and showed how one participant actuated their inhaler 77 times in just thirteen minutes, demonstrating the NC's ability to indicate dose-dumping [20]. A further study using the NC found an average median adherence of 77% [23]. The authors noted that the majority of participants found the NC acceptable, but two participants struggled with fitting their inhaler canister fully into the device [23], suggesting design limitations.

The reliability of the NC was tested alongside a newer monitoring device, the Doser, in two trials [24]. In the first trial lasting 4 weeks (but NC only tested for latter two weeks), the NC was found to be 93% accurate in comparison to manual recordings when actuated twice daily in a lab setting by clinical personnel. However, in the second trial lasting 4 weeks (but NC only tested for first or last two weeks of study) accuracy was 80% compared to patient self-report. Across the two studies, nine of the 48 NCs malfunctioned, with loss of data [24].

Research using the NC has also investigated the effect of providing patients with feedback on their medication use. The majority of literature on the NC comes from research as part of the 'Lung Health Study,' a five-year clinical trial investigating whether smoking cessation and bronchodilator medication can help prevent or delay the degradation of lung function in smokers with Chronic Obstructive Pulmonary Disease (COPD) [21]. A study of 251 adult cigarette smokers with mild to moderate airflow obstruction found that participants provided with feedback on their adherence through recordings by the NC actually improved in their adherence, compared to controls with no feedback [21].

Another aspect of the Lung Health Study conducted over a four-month period found that when not informing participants about the recording capabilities of the NC, 18% of subjects dose-dumped their inhaler. This 'dumping' phenomenon was removed once participants were informed [25]. A dumping phenomenon was recorded again by the NC in a further study, where 30% of a sample of 101 participants actuated their inhaler more than 100 times in a three hour period [15]. Another study using self report over a four month period found that of 95 participants, 73% stated they used their inhaler three times a day on average, yet NC data for 70 of these participants showed only 15% actually used their inhaler 2.5 or more times on average per day [26].

MDILog

Courtesy: Medtrac Technologies, Inc.

Fig.(2). An MDILog device (white box) attached to the back of a normal metered dose inhaler (MDI) [27] (image included with permission from Elsevier).

The MDILog (Fig. **2**.) was developed by Westmed Technologies Inc, Englewood, Colorado, USA [19]. The MDILog attaches onto the back of the plastic casing of a standard MDI [28].

The device is capable of recording actuations through a mechanical beam with a strain gauge, shaking of the inhaler with a movable magnet, and actual inhaling through a heated thermistor [22]. For each of these three sources of data, the date and time are recorded [22]. The device can store 1300 data logs in total [28], which can later be transferred to a PC using an infrared port, or wirelessly using a modem to transfer data directly from a patients home [28].

Features

- Records date and time of actuations
- Detects inhalation and shaking of inhaler
- Has a battery life of 6 months [22]
- Has an LCD display that shows feedback on adherence, or can alternatively be masked to limit feedback [29]
- Compatible with spacers

- Has an auditory tone that beeps to remind patients to use their inhaler, and beeps when a canister is empty [22]
- Data can be transferred via infrared port or modem
- FDA approved [22]

Limitations

- Cannot be sterilized to be used across multiple patients [28]
- Only compatible with a standard MDI
- Does not provide feedback to patient on inhalation technique

Relevant Literature

The reliability of the MDILog as a device has been tested across multiple studies. By comparing MDILog data with diary reports, one study found that 1200 actuation recordings for all three MDILog devices were 97%-100% accurate, inhalation was 82%-100% accurate and shaking identification was 86% to 95% accurate [27]. Another study tested 6 MDILog devices but found that one device repeatedly malfunctioned [30] and a further study compared the MDILog's reliability to two other devices by actuating two MDILogs twice daily for 30 days [31]. They found an accuracy of 90.1%, with occasional spurious recordings being noted. The researchers concluded the device is sufficiently accurate for monitoring adherence in clinical settings [31].

The MDILog has also been used in two different studies measuring adherence. The first found in a sample of 106 children with asthma that adherence over a month was 48% on average [32]. Similarly the second found a median adherence of 46% over one month in 75 children with asthma aged 8 to 16 [33].

Doser

Fig.(3). A Doser (right) attached to the top of an inhaler canister (left) [24] (image included with permission from Elsevier)

The Doser (Fig. **3**.) was developed by Meditrack Inc, Hudson, Massachusetts, USA [12]. The device is round and flat in structure and fits on top of a standard MDI canister, it also has an LED display to see feedback on adherence [31].

The Doser records actuations through an electromechanical switch that is activated when the user applies adequate pressure to the top of the inhaler, instigating actuation [34]. The device contains two different counters, one to count down the number of actuations remaining in the canister and another to count the number of actuations on a single day [31]. The second counter resets itself at midnight and stores the total number of actuations for each day in its internal memory [31]. The device will beep to tell a patient when an actuation has been recorded and also beeps when a canister is nearly empty [34]. Data cannot be downloaded from the device, it can only be written out manually [31].

Features

- Has 'Covert' and 'Overt' modes for LED display so feedback can be hidden if necessary [34]
- Battery life of 12 months [22]
- Beeps when there are fewer than 20 actuations left to alert patient that their canister is shortly in need of replacing [22]
- Compatible with spacers
- FDA approved [22]

Limitations

- Does not record date and time of actuation [31]
- Cannot upload data to a PC for review [31]
- Data is only stored for 30 days
- The battery cannot be replaced [22]
- Possible incompatibility with newer types of MDI canister [34]
- Does not detect inhalation [28]
- Does not detect shaking of inhaler
- Does not record data on technique nor provide feedback to patient on this

Relevant Literature

The reliability of the Doser has been extensively tested. A test of accuracy against two other monitoring devices for 30 days found two Doser devices to be 94.3% accurate with occasional recording of spurious actuations [31]. They also found the counter for amount of inhalations left in the canister sometimes went to zero prematurely [31]. A further study conducted three separate tests of reliability and found Doser accuracy ranged from 94%-97% [24]. Accuracy of

100% was reported in a study using 6 devices over 30 days [35], but another study using 16 Dosers over 61 months found that 8% had mechanical faults such as an unreadable display, battery failure and error messages [36].

A study of 27 children with asthma compared the Doser (301 devices used in total) as a measure of adherence against three other methods; self-report, mother report and canister weight [12]. Over six months, they found that child and mother reports on average gave adherence rates of 80%, canister weighing produced average adherence rates of 69%, but Doser devices reported average adherence rates of just 50% [12]. This led the authors to conclude that electronic monitoring is a significantly more accurate method of collecting data on adherence than self-report or canister weighing. However, the researchers stated that 61 (21%) of the Doser devices failed to retrieve data from their internal memory to be displayed on their LED screen [12].

SmartMist

The SmartMist was developed by Aradigm Corporation, Hayward, California, USA [37]. The SmartMist is a large device that encases nearly the entire MDI within it, leaving only the mouthpiece of the inhaler exposed [31]. It is compatible with standard MDIs [37].

The SmartMist records the date and time of every actuation [31]. Actuation of the inhaler occurs through inhalation; a plunger within the device pushes downward on the inhaler canister once a specific inspiratory flow rate (25 to 60 L/min) and volume (250 to 500mL) have been reached. [31]. As well as using its microprocessor and solid-state memory for recording actuations, inhalation flow is recorded before, during and after every use [38]. It can provide instant feedback on inhalation technique whilst a dose is being administered by displaying a flashing red light when inhalation is too rapid, a solid green light when inhalation is good and no light when inhalation is too weak [31]. This benefits adherence data as it can help indicate when doses have been taken but technique is good or poor. This can help a clinician or researcher to understand if poorly controlled asthma is associated with poor adherence or poor technique [31].

Data are transferred from the device to a PC via cable and from here it can be printed off so it can be viewed in a list or graph [31].

Features

- Records and provides instant feedback on inhalation technique [31]
- Records date and time of actuations
- Actuations are recorded through inhalation, preventing a patient from dose dumping using the device

- Data can be transferred to a PC
- FDA approved [39]

Limitations
- Large device, significantly increasing the size of the usual MDI

Relevant Literature

The reliability of the SmartMist was investigated in comparison to two other monitoring devices (MDILog and Doser as already mentioned) in a 30-day study where 6 SmartMist devices were actuated twice daily [31]. The researchers found that the SmartMist was 100% accurate with all actuation logs matching written recordings. This makes it the most accurate of the three devices. The authors suggested that due to the SmartMists excellent accuracy, it could potentially be useful in clinical research [31].

Smart Inhaler Tracker (Smart Inhaler Generation 1)

Fig.(4). A Smart Inhaler Tracker with canister inserted. (image included with permission from Nexus 6, www.smartinhaler.com/).

The Smart Inhaler Tracker (Fig. **4**.) was developed by Nexus 6, Auckland, New Zealand [40]. The device consists of a plastic casing, with slightly different shapes available for different medication canisters [40]. The device maintains a similar shape to that of a normal MDI casing, with a larger size to allow room for the battery and electronics [35].

When a patient presses downwards and applies pressure to their inhaler, the canister connects with a switch within the device, resulting in the recording of a time and date stamp for the actuation [34]. This process happens for every actuation of the inhaler, with the device capable of recording 1600 data logs in total [34]. Actuation recordings can be transferred to a PC through a USB (Universal Serial Bus) cable, where 'connection centre' software takes data from the device and uploads it to an online database where it is kept in

password protected storage, to be viewed by either the patient, clinician or researcher or other person with granted access [40].

Features

- Records date and time of actuations
- Different shaped cases available for different medication canisters
- Compatible with spacers [41]
- Reusable [34]
- Data can be transferred to PC via USB
- Audio Visual Reminder Function (AVRF) can be built in to provide feedback to patient and remind them to use their inhaler. Alarm can beep every 30 seconds for up to 60 minutes and LED light can display green light before actuation and red light after [42]

Limitations

- Needs specific casings designed for specific drugs and is therefore not a generic monitor that fits all MDIs
- Does not detect inhalation [43]
- Does not detect shaking of inhaler
- Does not record data on technique nor provide feedback to patient on this [43]
- No display to provide detailed visual feedback on when last dose was taken, or how many doses have been taken in total.

Relevant Literature

A number of studies have assessed the reliability of the Smart Inhaler Tracker. In one study, 10 Smart Inhaler Trackers were tested through the researchers actuating them twice daily for 30 days [35]. They found five to be 100% accurate, but one failed to record the very first dose and the remaining four all failed to record the first two doses. However, after the first two doses all 10 were 100% accurate with no spurious recordings. It was later discovered that the failing of some devices to record the first one or two doses was due to the canister not being inserted far enough into the device [35]. The same study also tested the Smart Inhaler Tracker's ability to indicate dose dumping, by taking 6 devices and actuating each 30 times in a row over a very short period. They found all to be 100% accurate [35].

A prolonged study in contrast to other short-term validation studies tested the accuracy and reliability of the Smart Inhaler Tracker over a 24-week period [44]. The authors tested 22 devices in total at 0, 8, 16 and 24 weeks by simulating both low use (two actuations separated by 10-20 seconds each) and high use (eight actuations separated by 10-20 seconds each). They found overall accuracy in recording

the number of actuations was 99.7% and accuracy in recording the date and time of actuations was 99.3% [44].

An extensive study found that of 2642 Smart Inhaler Trackers dispensed, 2498 (94.5%) successfully connected to a PC and uploaded a complete data set [40]. Furthermore of 2549 devices returned by patients, 2498 (98%) successfully uploaded complete data sets. Devices that failed were mostly due to fluid immersion. The authors concluded that the Smart Inhaler Tracker is a sufficiently reliable monitoring devices to be used for measuring adherence in real-world settings [40].

One study used the Smart Inhaler Tracker in a feasibility test of bronchial hyper-responsiveness (BHR) to manage asthma [45]. 14 adults with asthma had their ICS use monitored and were tested for BHR on three separate occasions over size weeks. They found that 2 of the 10 Smart Inhaler Trackers they used failed to upload data (20%). They also received feedback from patients about devices that could be used to monitor their medication use. One patient stated "Knowing that it was recording dosing time made me more conscious of taking (my) medication" whilst another said "Knowing someone is going to check the (dosing) times makes you comply" [45].

The Smart Inhaler Tracker has been utilised in a number of studies investigating adherence in asthma. A 24 week randomized controlled trial with 111 patients with asthma aged 16-65 investigated whether a combination inhaler containing ICS and long acting beta agonists significantly improved adherence compared to separate standard inhalers [46]. The Smart Inhaler Tracker was used to monitor adherence and over the final 6 weeks of the trial found no significant difference in adherence between patients on combination therapy or separate [46].

An investigation into the effect of an audio-visual reminder on adherence in 110 participants with asthma aged 12-65 found that after 12 weeks adherence was significantly higher in the audio-visual reminder condition (93%) than in the control group (74%) suggesting that the Smart Inhaler Tracker with this capability to remind patients enabled, may actually help improve adherence as well as record it [42].

A study of 51 children with asthma compared adherence recorded through the Smart Inhaler Tracker to adherence as reported by parents and in questionnaires they were required to complete on their child's medication taking [18]. Parental reports (85.1%) and questionnaires (84.2%) both significantly overestimated inhaler use as average adherence rates were shown by the Smart Inhaler Tracker to be 70.5% [18]. A recent study of 93 children found a median adherence of 92% over 3 months using the Smart Inhaler Tracker with 94% of parents stating that regular inhaler use would prevent their child from getting worse [47]. This finding of high adherence was likely to be due to the education and follow up of the participants [47].

SmartTrack (Smart Inhaler Generation 2)

Fig.(5). A SmartTrack device (black) clipped around a standard MDI (purple). (Image included with permission from Nexus 6, www.smartinhaler.com/)

The SmartTrack (Fig. **5**.) was developed by Nexus 6, Auckland, New Zealand [34]. The device securely clips around a standard MDI and consists of an LCD screen capable of displaying information about medication taken, battery level and various settings. Surrounding the device are 4 square buttons that can be pressed to navigate through the device's interface. Like its predecessor, different shaped devices are available for different medication types [34].

The SmartTrack records the date and time of actuations, MDI insertion/removal and setting changes such as turning reminders on/off [48]. Actuations are recorded using an optical dose counter [49]. A light transmitter and light receiver and placed at opposite ends of the inside of the device, both below the canister. When the inhaler canister is depressed, it blocks the light from the transmitter reaching the receiver, allowing for the dose counter to register this as an actuation and create a date and time stamp to accompany it [49].

Data can be transferred from a SmartTrack to a PC via a USB cable where 'connection centre' software takes data from the device and uploads it to an online database where it is kept in password protected storage, to be viewed by either the patient, clinician or researcher or other person with granted access [34,40]. Data from the SmartTrack can also be viewed on the 'SmartinhalerLive' smartphone application, which can display adherence data in graphs or tables to allow the viewer to see inhaler use and missed doses over a period of time.

Features

- Records date and time of actuations, canister insertion/removal and turning reminders on/off
- Different shaped devices are available for different types of medication

- Compatible with spacers
- Reusable
- LCD screen to display feedback to the patient on when their inhaler was last used, battery life and settings
- Choice of ringtones available for auditory reminders [34]
- Data can be transferred to a PC where it can then be viewed on an online database or on a smartphone
- FDA approved [50]

Limitations

- Does not detect inhalation
- Does not detect shaking of inhaler
- Does not record data on technique nor provide feedback to patient on this
- Adds significant bulk to a standard MDI

Relevant Literature

To date, only one published study has used the SmartTrack device. This study assessed both the reliability of the SmartTrack as well as patient attitudes towards it [48]. Three reliability tests were performed. The first test investigated the accuracy of actuations logs and device functions such as ringtones at correct reminder times, displayed information on 'last puff taken' and the data/time on the device. They found 9/10 devices performed all tasks 100% accurately, with one device failing to record any actuations or any canister insertions/removals. The second test simulated actual patient use in the nine fully working devices by actuating two puffs twice a day for two days, followed by mimicking dose dumping by actuating 30 doses in quick succession. They found 6/9 devices to be 100% accurate, with one device having inaccurate actuation times compared to diary entries and the remaining 2 devices experiencing minor errors deemed as 'acceptable' to the researchers [48].

The final test consisted of the eight still fully operational SmartTrack devices being assigned to eight adults with asthma [48]. Participants were instructed to take their medication at their usual frequency and to record in a diary whenever they actuated their inhaler for seven days. Overall accuracy of actuations recordings for this period was found to be an average of 95.6% for the 8 devices. The six SmartTracks that had been set up to remind patients all successfully rang on time and were all silenced appropriately [48].

This study also asked for feedback from participants in the third test on their attitudes towards the SmartTrack device [48]. All patients rated the device as easy to use. Some of the comments provided by participants included "Buttons are small and sometimes hard to register", "I quite

liked having a reminder", "It was a bit bulky to take away for a weekend" and "(Reminders) rang too regularly perhaps once every 5-10 minutes; short ringtones were good" [48].

SmartTouch AV (Smart Inhaler Generation 3)

Fig.(6). A SmartTouch AV device (white) clipped around a standard MDI (red). (Image included with permission from Nexus 6, www.smartinhaler.com/)

The SmartTouch AV (Fig. **6**.) was developed by Nexus 6, Auckland, New Zealand [51]. The device clips around a standard MDI in the same way as its predecessor the SmartTrack, meaning it simply fits around the usual inhaler casing which houses the canister [51]. The device consists of a touch-screen display capable of providing information on medication use, time, battery level and settings such as notifications. The touch-screen allows for the user to directly interact with the display through pressing icons, rather than by pressing buttons next to the display as is seen on the SmartTrack [51]. Like the first and second generation Smart Inhalers, different shaped devices are available for different medications [51].

The SmartTouch AV records the date and time of every actuation [51]. Actuations are recorded using the same process as the SmartTrack inhaler, an optical dose counter consisting of a light transmitter and light receiver are placed within the device [49]. When the inhaler canister is depressed, this breaks the light between the transmitter and receiver, resulting in the dose counter recording this as an actuation along with the date and time [49]. The SmartTouch AV has a memory capable of storing up to 4096 actuation logs [51].

Data from the SmartTouch AV is transferred to an online database where it is stored in password protected storage [52]. Data can be transferred through three methods; firstly, the 'Smart Hub' can be placed in a patient's home and requires no existing Internet connection due to a built in modem [52]. Data is automatically transferred using the Smart Hub whenever a SmartTouch AV is in range. Alternatively, data can be transferred using the 'Smart Key', a USB peripheral that can be plugged into an internet-connected PC via a USB port. This works in the same way as

the Smart Hub and uploads adherence data whenever the SmartTouch AV is in range. The final method for uploading data is via 'Smartinhaler Mobile', the dedicated Smartinhaler application for smartphones and tablets. The Smartinhaler Mobile application pairs a phone or tablet with a SmartTouch AV device through a Bluetooth connection, allowing for automatic uploading of data whenever the two devices are in range of each other and the phone or tablet has internet access [52]

As mentioned, the SmartTouch AV device can be accompanied by the Smartinhaler Mobile smartphone application [52]. This allows for a patient's smartphone to display information on a patients inhaler use over a period of time such as a week or a month. It also allows for a patient to stay updated on their inhaler use through a device that would not usually be associated with their asthma, instead of a through a feedback system attached to their inhaler. The Smartinhaler Mobile application is currently available for iPhone, iPad and Android devices [52].

Features

- Records date and time of actuations, canister insertion/removal and turning reminders on/off
- Different shaped devices are available for different types of medication
- Compatible with spacers
- Reusable
- Battery life of 1-3 months depending on usage
- Has a touch-screen to display feedback to the patient on when their inhaler was last used, battery life and settings and to allow for the patient to directly interact with the device interface
- Different ringtones available for customisable reminders [52]
- Multiple methods for automatically and wirelessly transferring adherence data
- Dedicated Smartphone application capable of transferring and uploading data and displaying feedback on adherence.

Limitations

- Does not detect inhalation
- Does not detect shaking of inhaler
- Does not record data on technique nor provide feedback to patient on this
- No published peer-reviewed literature on accuracy

Relevant Literature

No relevant literature currently available.

Propeller (Formerly Asthmapolis)

Fig.(7). A Propeller device (white) attached to the top of the canister of a standard MDI. (Image included with permission from Propeller Health, www.propellerhealth.com)

The Propeller device (Fig. 7.) was developed by Propeller Health, Madison, Wisconsin, USA [53]. The Propeller device is a circular cap that 'snaps' onto the top of a standard MDI canister [54]. This cap can be adjusted for different sized canisters by adjusting the position of the sensor slightly to achieve a tight fit [54]

The Propeller device records the date and time of every actuation using it's internal clock and also records the GPS (Global Positioning System) location [54]. Actuations are initially registered and identified by the device through the use of a magnet and magnet sensor [55]. When the inhaler canister is depressed, this brings the magnet within the device towards the magnet sensor. When the magnet and sensor touch, this acts as a switch and results in a voltage change in the device, which is then recorded as an actuation along with a date/time and GPS stamp [55].

The Propeller device can transfer adherence data in three different ways [54]. Firstly, via Bluetooth connectivity to a smartphone with data automatically and wirelessly uploaded via the patient's phone to the Propeller Health online database. The patient can then receive feedback on their adherence by viewing information on their smartphone using the dedicated Propeller Health smartphone application [54]. However, if the patient does not have a Smartphone, a 'hub' can be placed within their home to be paired with their Propeller device to automatically upload adherence data. For these patients, they can receive feedback on their adherence through e-mail. If a patient does not have e-mail, they can receive feedback by phone call. If there is neither a smartphone nor a 'hub' within sufficient proximity of a Propeller device, it will hold the data in its memory (which can hold up to 3900 logs) until a smartphone or 'hub' is available to transmit data to [54].

The Propeller Health smartphone application is a key part of the Propeller system, as the Propeller device itself does not have a display or any buttons [53]. The smartphone application is available on the App store for iOS devices (iPhone and iPod touch) and on the Google Play Store for various Android devices. The application is available in both English and Spanish, but is currently only available for download in the USA. The application can display information to a patient in a visual form, such as trends of use, date/time and location of actuations [53]. The application also sends a message to the patient when they use their rescue medication such as "We see you used your rescue medication. We hope you're okay, when you're feeling better, enter your trigger information. Like were you near a cat, was there mould, or was it cold outside?" this helps build a record of specific triggers for a patient's asthma, with the aim of improving patients self-management of their asthma over time [53].

Features

- FDA and Health Insurance Portability and Accountability Act (HIPAA) approved [53]
- Records date and time of actuations
- Records GPS of actuations
- Compatible with spacers
- Reusable [34]
- Suitable for users with/without smartphones and with/without email
- Battery life of 40 days (recharged via USB connection) [54]
- Feedback on adherence via smartphone or email
- Prompts to patients to describe triggers via smartphone application
- Sends messages to patient to educate on better inhaler use, helping them to understand particular triggers for their own asthma based on previous inhaler use recorded by the device.

Limitations

- Only available in the USA
- Does not detect inhalation
- Does not detect shaking of inhaler
- No published peer-reviewed literature on accuracy
- Does not record data on technique nor provide feedback to patient on this

Relevant Literature

Research using the Propeller device is still in its infancy. A pilot study using an earlier version of the Propeller sensor with 30 participants found that after 4 months using the device and receiving feedback on their asthma management, 75% of the participants had an Asthma Control Test (ACT) score of 19 or above (19 being controlled asthma) [56]. At

the beginning of the study, only 38% had such an ACT score [56].

An on-going study is also being carried out with 498 asthma patients in California, USA, where the latest Propeller sensor has been assigned to half the participants [57]. No results have been published so far, although the researchers have reported that participants using the Propeller device are on track to save an average of $700 in healthcare costs in comparisons to the previous year [57].

Table 1. Summary of features for EMDs in asthma treatment

Device	Re-usable	FDA approved	Spacer Compatible	Records Date and Time of Actuation	Detects Inhalation	Detects Shaking of Inhaler	Record and Feedback Information on Inhalation Technique	Reminders for Patients	Records GPS Location of Actuation	Device Screen to Display Information	Data Transferable to PC/Online Storage	Dedicated Smartphone Application
Nebulizer Chronolog		✓		✓							✓	
MDILog		✓	✓	✓	✓	✓		✓			✓	
Doser		✓	✓					Beeps for canister nearly empty		✓		
SmartMist	Info. not available	✓	Info. not available	✓	✓		✓			✓	✓	
Smart Inhaler Tracker	✓	Info. not available	✓	✓				✓			✓	
SmartTrack	✓	✓	✓	✓				✓		✓	✓	✓
SmartTouch AV	✓	Info. not available	✓	✓				✓		✓	✓	✓
Propeller	✓	✓	✓	✓					✓		✓	✓

Other devices

There are notable examples of devices built for inhalers other than a standard MDI. The INCA (Inhaler Compliance Assessment) device was developed by Vitalograph Ltd and is compatible with a Diskus[TM] inhaler (Accuhaler[TM] in the U.K.) [58]. This device uses a microphone to record acoustic signals capable of detecting peak inspiratory flow rate (PIFR) and actuations in patients. Like other devices this data can later be uploaded to a PC via USB connection and software can be used to calculate date and time of doses [58]. The INCA device can measure both temporal adherence as well as technique [59]. Validation of this device has been carried out in 69 patients with asthma where a close correlation was found between audio recordings of dose and doses taken. Further investigation demonstrated a close correlation between acoustic energy of exhalations into the inhaler device and the amount of drug removed in that particular dose [59].

Another device is the Diskus Adherence Logger (DAL), this device consists of a small postage stamp sized module that is attached to the outside of a Diskus inhaler [60]. It detects whenever the Diskus lever is pushed into the correct position for actuations. The DAL device itself can be inserted into a USB port on a PC, allowing data to be transferred to dedicated software [60].

FUTURE ISSUES

Stakeholder Involvement and Intervention

A key issue to consider in adherence monitoring is to whom the adherence data is available and the potential issues this may cause. The Smart Inhaler and Propeller devices all upload adherence data to an online database where it can be viewed by any person with granted access; this could be the patient, a family member, carer, friend or a medical professional such as a GP or Asthma nurse [34,40,54].

In the case of a healthcare professional, this availability of adherence data in a regularly updated form raises some interesting questions about their involvement and responsibility to intervene. Access to patient data allows a medical professional to interpret how adherent a patient is to their prescribed treatment with relative ease and in far greater detail than through their clinic visits.

An example of where the value of adherence data at this level of detail is demonstrated comes from a recent real world asthma clinical trial using EMDs, in which adult patients commonly both underused and overused their inhaled treatments [61]. The authors reported extreme overuse of beta-agonists (32 or more actuations a day) in 40 (26%) of their 152 participants on standard treatment [61]. This creates a number of potential issues, such as the potential responsibility of a professional to intervene as well

as their chosen method for doing so. Furthermore an exact threshold for both underuse and overuse of inhaled medication needs to be established whereby a medical professional has an obligation to intervene and contact the patient.

Once it is established *when* and *where* an intervention is necessary, the next consideration is *what* this intervention should actually be. Many studies have demonstrated interventions to improve adherence, such as education on self-management and feedback of adherence data, but there is little agreement over what is most effective and therefore recommended [62]. Furthermore, it needs to be addressed how the additional time spent using this adherence data for interventional purposes could be suitably assigned by commissioners and funders as separate from 'standard' asthma care. Successful uptake by health care professionals may be unlikely without appropriate means to claim for extra care costs [63].

As methods of intervening are determined, it is important to also consider the health literacy of patients, carers, and family for whom interventional information may be communicated to; information must be portrayed in an easy to understand way and accessibility to services such as the Internet, computers and smartphones must be achieved.

Novel Methods of Communicating Adherence Data

With new information readily available on adherence to asthma medication there is opportunity to improve understanding of adherence by patients, but it is important to consider how best to communicate this information. All the devices discussed (apart from the Doser) are capable of uploading data to a PC (see Table **1**). This allows for information to then be displayed as a graph or table, to either be printed out or viewed on screen, so that a patient can either review the data alone, or with another individual such as their GP or asthma nurse.

This standard method of communicating adherence data back to a patient has been used with some success with studies reporting an improvement in patients at high-risk of non-adherence [21,25,41,64]. However, it is important to investigate new and alternative methods of feedback and communication to attempt to utilise this wealth of data. With the recent surge in smartphone based applications and compatible devices for fitness and health [65] it appears a natural progression for asthma research to explore the potential for integration of smartphones in asthma treatment, through utilising them as a method of communicating feedback on adherence to patients.

Smartphone integration for asthma management has been investigated [66–70] with mixed results. One six-month trial of 288 adolescents and adults with poorly controlled asthma

found that smartphone based monitoring had no significant effect on asthma control and self-efficacy in comparison to paper based monitoring [69]. These were measured using the asthma control questionnaire (ACQ) and the knowledge, attitude, and self efficacy asthma questionnaire (KASE-AQ) [69]. However in this study participants were required to input their symptoms, drug use and peak flow readings manually to either a smartphone or on paper, with an asthma nurse contacting patients in the smartphone group with peak flow recordings in 'red' or 'amber' zones [69]. This is different to an EMD automatically syncing recorded data with a mobile phone, such as in the SmartTouch AV and Propeller devices. A similar study investigated the feasibility of a text-based system as a method of generating daily reports on a patient's asthma [70]. Results showed a high response rate to text messages of 81%-97% and demonstrated that participants felt using the system helped improve their awareness of symptoms as well as promoting a greater sense of control and better adherence to their asthma [70].

Along with the smartphone integration and automatic syncing seen in the SmartTouch AV and Propeller devices, another recent technology exists using a game-based system based on an Android platform to reinforce adherence. 'Geckocap' [71] are a new start-up company who have developed both a monitoring device to clip to the top of a standard MDI, along with a smartphone application aimed at children with asthma. The application automatically updates with the most recent inhaler use and allows parents to set goals and award prizes through the application for good adherence. Similar approaches, attempting to 'gamify' improved health management include 'MangoHealth' [72] and 'PatientPartner' [73].

Varying User Needs

When designing an EMD the needs of different patient groups must be taken into consideration. This is particularly the case in asthma which can affect children, adolescents and adults. Moreover inhaler adherence is equally important in Chronic Obstructive Pulmonary Disease (COPD), a condition predominantly affecting the elderly. For example, a smartphone application to work alongside the monitoring device may be an effective system for adolescents, as recent statistics show that in the UK around 81% of 12-17 year olds own smartphones, with this figure predicted to rise to 96% by 2017 [74]. However, only 13% of people aged 65+ currently own smartphones, with still less than half of this portion of the population expected to own smartphones by 2017 [74]. It is important to recognise that whilst smartphone integration could be a viable option for technology-aware users, it should not be assumed that all people will be comfortable or capable of using the same technological solutions.

An example of where meeting the needs of different user groups has been established is the Propeller device, where feedback on adherence can be communicated back to patients through a smartphone application, e-mail or phone call [54]. This allows the system to cater for different needs and recognises that different users may not have access to certain technologies and services.

There is still a need to take the potential low socio-economic status of users into account in the development and provision of EMDs, particularly as technology becomes more advanced. Expensive technologies may be unaffordable and inaccessible for a portion of the target population [75] and there is also evidence that health technologies may be not be adopted as quickly by ethnic minorities [76]. This is particularly important as certain ethnic groups may be disproportionately affected by asthma [77] or may have particularly poor asthma outcomes [78–80].

Barriers to Adoption

If EMDs were to be fully established in asthma care, there are several potential barriers to be overcome. These barriers include patient attitudes to treatment and responsibility for data monitoring and protection.

Patient Attitudes

Research on EMDs to date has largely been clinically-focused in nature. Although investigating the reliability and accuracy of a monitoring device are essential, research and development processes must also consider the user. This would involve patient attitudes towards the devices including factors such as their usability, their portability and practicality, their social acceptability [81], and how comfortable a patient would feel having their medication taking behaviour recorded in this way. These are important factors to consider for successful uptake and long-term use of these devices, which have not yet been investigated..

The only notable examples where patient feedback has been obtained are in a study using the Smart Inhaler Tracker [45] and a study investigating the accuracy of the SmartTrack [48]. However, even these studies simply gathered this data as a secondary aim alongside their overall main objective. Both studies also used samples of adult patients. No research on EMDs for inhalers to our knowledge has considered the attitudes of the age group where asthma is most prevalent – children and adolescents.

Data Monitoring and Protection

Recording data on patient health and adherence to their medical regimen is a sensitive source of information where a suitable security and privacy framework is required. If data is unsecure and is leaked or hacked this could have serious consequences for the patient as personal and private

information could become available to employers, health insurers or other individuals who would not usually have granted access [82]. Furthermore, there could be severe implications for either the responsible health professionals or IT providers who could be charged with violating privacy legislations and incur serious legal penalties as a consequence [82].

With the integration of smartphones, wireless automatic uploading of data, and online databases as seen in the Propeller and SmartTouch AV devices, adherence data is commonly being stored in the 'cloud'. Although there is debate over the correct definition of 'the cloud' it can be described as a new paradigm for computing infrastructure where the location of the infrastructure is changed from being based in hardware and software to being based in the network [83].

Storing sensitive and personal health information in the 'cloud' creates a number of issues. Firstly, although data can be described as being 'stored in the cloud' the cloud itself is run from a data centre. Sensitive health data stored here must be sufficiently secured and protected through strong cryptographic encryption so that it cannot be leaked from within it [82]. Furthermore, the data centre is likely to require maintenance, so a system needs to be established to allow these processes to be achieved without an administrator actually accessing the sensitive patient data [82].

The second issue arises from the security of the PC and network infrastructure of the end-user [82]. This could be the patients home PC, a PC at a doctor's practise or a PC at a hospital or health centre. These systems often lack sufficient protection and can be vulnerable to threats such as malware attacks where passwords and data could be stolen and leaked to other unidentified and unauthorised sources [82]. Although this can be an issue for patients, it could be considered an even greater issue for doctors who are likely to see multiple patients. Doctors who run their own practise often lack both the time, knowledge and ability to maintain and regulate effective security and protection for their own IT infrastructure. This could therefore pose a serious risk and sensitive data from multiple patients could be hacked and leaked [82].

The third issue to consider relates to the use of smartphones. With the introduction of smartphone applications to wirelessly sync with monitoring devices such as the SmartTouch AV and Propeller, this again relies on the users own personal smartphone being free from viruses and malware which could intercept or access adherence data outside of the monitoring devices dedicated smartphone application.

There is therefore a need to consider how patient data should be stored and how it should be appropriately protected and secured so that only those with granted access to the information are able to privately view it.

Future Research

Although research to date has focused largely on the reliability and accuracy of devices, there is still further work required in this field as devices develop and gain new features and capabilities. For example, the potential relationship and benefit to adherence of the Propeller devices' ability to record the GPS location of actuations remains un-tested. Furthermore, the ability of the SmartTouch AV device and Propeller device to wirelessly and automatically sync adherence data via Bluetooth to various technologies such as smartphones and modems also lacks published literature on its effectiveness and reliability.

Future work also needs to consider the user. Qualitative research needs to specifically investigate the attitudes of different user groups such as children, adolescents, adults and the elderly to determine how the needs of these populations differ and to help identify potential barriers to adoption such as unease about recording of data and whom data should be shared with. The attitudes of key stakeholders in asthma management to EMDs needs establishing including GPs, asthma specialists, asthma nurses, pharmacists and commissioning groups. Determining how these groups view monitoring in asthma is crucial for the viable widespread adoption of the technology. Establishing when and at what point stakeholders feel they have an obligation to intervene with a patient, if this data on adherence is available, is crucial.

The effect electronic monitoring may have on adherence itself has been investigated previously, where it has been shown EMDs can not only accurately record adherence but improve it as well [21,25]. However, the differential effect of being monitored alone versus being monitored *and* receiving feedback has not been established. These two factors need to be isolated and investigated in the same study with the same sample to determine exactly how much each affects adherence.

CONCLUSION

EMDs for asthma treatment are rapidly developing, and will continue to develop, with new features including smartphone integration, wireless data transfer, cloud storage and GPS all advancing device capabilities and assisting introduction of EMDs into everyday treatment for asthma patients.

We have provided a review of EMDs and a summary of the relevant literature relevant to their reliability and accuracy. It has been highlighted that many other factors related to these devices have so far been largely overlooked.

The needs and requirements of different user groups such as children, adolescents and the elderly must be identified to make EMDs compatible with their treatment. Furthermore, access to data by key stakeholders in a patients asthma treatment, the responsibility of these individuals to intervene as well as the method of intervention need determining. Sensitive information may be recorded by EMDs and further work on how data is stored and protected is also of importance.

These key issues when considering the uptake of EMDs have been discussed in this review, including areas of future research.

ABBREVIATIONS

ACQ	=	Asthma Control Questionnaire
ACT	=	Asthma Control Test
AVRF	=	Audio Visual Reminder Function
BHR	=	Bronchial Hyper Responsiveness
COPD	=	Chronic Obstructive Pulmonary Disease
DAL	=	Diskus Adherence Logger
EMD	=	Electronic Monitoring Device
FDA	=	Food Drug Administration
$F_E NO$	=	Fractional Exhaled Nitric Oxide
GPS	=	Global Positioning System
HIPAA	=	Health Insurance Portability and Accountability Act
ICS	=	Inhaled Corticosteroids
INCA	=	Inhaled Compliance Assessment
KASE-AQ	=	Knowledge, Attitude, and Self Efficacy Asthma Questionnaire
MDI	=	Metered Dose Inhaler
NC	=	Nebulizer Chronolog
PC	=	Personal Computer
SABA	=	Short-Acting Beta Agonists
USB	=	Universal Serial Bus

CONFLICT OF INTEREST

The authors confirm that this article has no conflicts of interest.

ACKNOWLEDGMENTS

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