The Role of Connected Inhalers in Improving Usability and Adherence in Respiratory Disease

Recent data suggest that 339M people globally have asthma, resulting in 425,000 deaths annually, many of which would be preventable with access to medication and appropriate healthcare[1]. Even in countries with high standards of living, well-established healthcare systems and proper medication availability, unnecessary deaths still occur. In fact, a recent report suggests that around two-thirds of asthma deaths are preventable in the UK[2]. Although several factors contribute to a failure to manage treatment effectively, failure to take medication as prescribed[2] is a key issue. An estimated 50 per cent of people with asthma fail to do this – a figure that may well understate the problem – and is well below the 75-80 per cent adherence levels required to improve asthma control significantly[3]. Furthermore, many users who intend to take their medication fail to do so because of poor inhalation technique. Studies suggest that at least a third of inhaler users have a technique that adversely affects the delivery and/or absorption of the drug in the lung[4], and that this rate has not changed over the past 40 years. This article aims to consider why patients don't take their respiratory medication and how adherence to inhaler medication can be improved.

Medication Non-adherence: Two Key Factors

For asthma, there are two primary aspects of medication non-adherence to consider:

- First, patients may fail to take their medication for a variety of reasons. There may be a lack of belief in the efficacy of the drug, concerns about real and perceived side-effects, high out-of-pocket costs or simply forgetting to take the medication. As asthma symptoms are often episodic, many patients may feel they can skip doses to save money or reduce side-effects. Furthermore, patients may rely too much on using their reliever medication when experiencing asthma symptoms, rather than regularly taking their prevention medication. Failure-to-use is a complex issue but, as discussed below, developments both in technology and understanding human behaviour may offer the potential to address this.

- Second, it is well known that inhalers are prone to use errors[5], notably dose preparation errors (where the user fails to load or prime the device) and inhalation errors (where the user fails to perform the correct inhalation technique for effective delivery of the drug to the lung). So even when a patient intends to take their medication, they may not receive an effective dose. These factors make inhaler use more challenging than the use of other drug delivery devices such as insulin pens and autoinjectors. The reduction of use errors has therefore been a particularly important theme in the evolution of inhaler design. In a presentation made more than 10 years ago at RDD (a leading respiratory conference), Dixon and Simpson[5] summarised the literature reporting on inhaler use errors. They suggested that the majority of use errors should be addressable through application of the principles and methods of usability engineering and inclusive design. These, combined with the adoption of novel deaggregation/aerosolisation technologies, can enable better inhaler designs to fit with users' typical behaviour. While use errors continue to be an issue for inhaled therapy, more recent dry powder inhaler designs such as the Ellipta device developed by GSK, the NEXThaler developed by Chiesi and breath-actuated pressurised metered-dose inhalers (pMDIs) such as the Teva Easi-Breathe have come close to optimised designs, showing lower use errors than comparable device types[6,7,8]. Open-Inhale-Close designs such as Chiesi NEXThaler and Sun Pharma Starhaler represent an idealised design, with the fewest user steps and the ability to avoid errors such as double dosing or dose loss, if inhalation does not take place. Wider adoption of these newer device designs should reduce the overall use error rate observed.

With a strong focus on the use of human factors engineering to guide device design

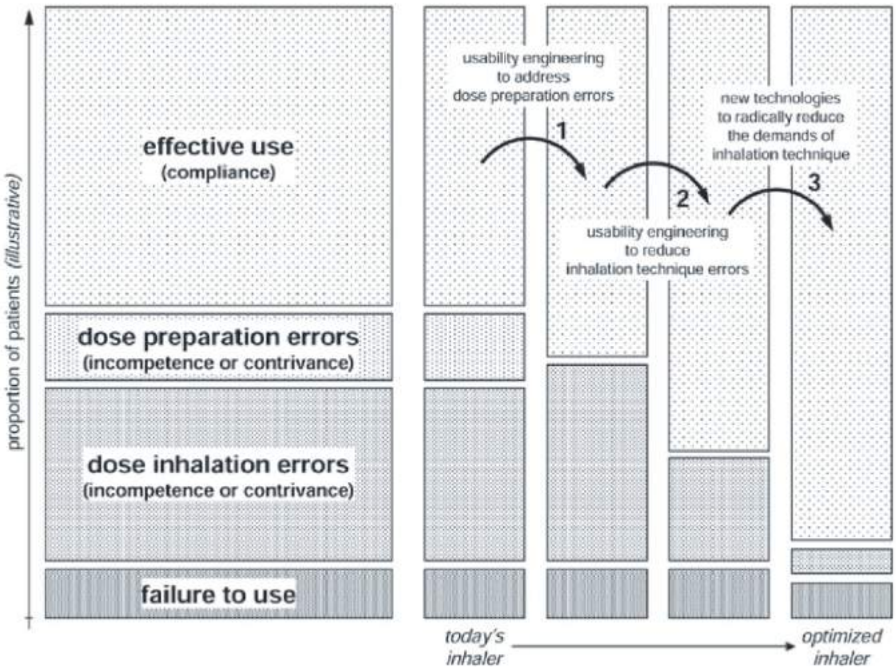

Figure 1

(notable since the FDA published guidance in 2000[9]), there has been a reduction in use errors for many drug delivery devices, as predicted by Dixon and Simpson. Now, more attention can be paid to addressing failure-to-use and as Sheldon Moberg from Amgen commented at a conference in 2012 "To address adherence, [we] need to focus on 'want to use' as well as 'can use'[10]." In their work, Dixon and Simpson made little consideration of failure-to-use. They assumed that the principles of inclusive design might influence willingness to use, but overall, this was a different and more complex challenge that goes beyond inhaler design.

Subsequent years have seen two significant developments that might help address the issue of failure-to-use: 1.) the arrival of connected devices and digital health; and 2.) the development of psychological models that allow a better understanding of human behaviour and the interventions that can influence behavioural change. As discussed below, connected devices and associated digital services provide a useful means of supporting behavioural change.

The Impact of Behaviour Change on Medication Adherence

At its core, non-adherence is a behavioural issue, which can be addressed by designing interventions that influence behaviours that support or hinder medication use. However, focusing solely on the patient misses a large part of the issue, as it is essential to consider other factors that influence their behaviour and their capacity to adhere to their treatment regimen. Sabate (2003)[2] identified five interacting dimensions that affect adherence: 1.) social and economic factors; 2.) healthcare team and system-related factors; 3.) condition-related factors; 4.) therapy-related factors; and 5.) patient-related factors. These dimensions can influence adherence in many different ways – i.e. not having the financial means to pay for medication, the knowledge to understand the importance of medication use, or the right training and support and motivation from healthcare professionals or other caregivers. To be effective in improving adherence, an intervention needs to target one or more of these factors.

Although behaviour change models are in everyday use, the COM-B model has gained popularity in recent years.

It was developed by the Centre for Behaviour Change at University College London from a rigorous assessment of existing behavioural change research and frameworks. It proposes that the performance of a particular behaviour requires someone to have the capability, the opportunity, and motivation to do so.

- **Capability** includes both the psychological and physical capacity to engage in an activity, including knowledge, skill and memory.
- **Motivation** relates to the neurological processes that operate both consciously and subconsciously to direct behaviour, including habits, emotions and analytical decision-making such as goal setting.
- **Opportunity** refers to the factors that lie outside an individual that make the behaviour possible or trigger its performance. Opportunity includes physical environment and resources as well as social and cultural aspects of life such as stigmas, taboos and beliefs that might encourage or discourage behaviour.

As shown in Figure 2, these components of the framework interact to stimulate or modulate behaviour, and conversely, enacting a response might then influence these components to create a virtual or vicious circle. The model has been applied to a range of situations, including smoking cessation, encouraging testing for transmittable diseases, use of hearing aids and medication adherence.

Although COM-B was developed as a model of behaviour, its power in situations such as addressing non-adherence is that it provides a basis for designing interventions targeting behaviour change. With this in mind, Michie *et al.*[12] developed a Behaviour Change Wheel that links the COM-B model to nine intervention functions and seven policy categories identified in the assessment of existing behavioural change frameworks, as shown in Figure 3.

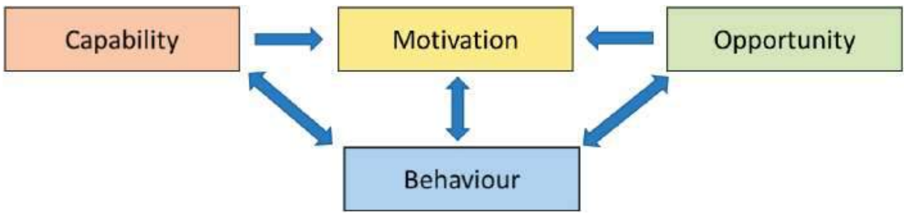

Figure 2: The COM-B Model of Behaviour

Jackson *et al.* describe how the COM-B model can be applied to medication adherence[13]. They used three comprehensive reviews of medication adherence studies to identify and map the different factors associated with adherence. They found most factors mapped directly onto a sub-component of COM-B, but depression, substance abuse, marital status and forgetting show a more complex association impacting several areas of the COM-B model. This complexity is to be expected as marital status, for example, can impact social support, cost and access. The authors suggest a three-step process to developing an adherence intervention:

- First, the use of secondary and primary research to identify the factors associated with non-adherence within the target population and map these to the sub-components in the COM-B model.
- Second, identification of intervention types and behaviour change techniques appropriate for the sub-relevant components, for example using the taxonomy developed by Michie *et al.*[14]
- Third, as an understanding of the effectiveness of different BCTs in influencing the COM-B sub-components is better established, the intervention can be optimised.

In other published research, COM-B has been applied to adherence in several disease areas, including asthma[15], COPD[16], hypertension[17], oncology[18], and growth hormone deficiency[19].

Digital services provide an ideal service structure to support medication adherence. They allow support to be delivered to patients remotely via apps and portable devices, information to be gathered and shared between key stakeholders including the patient, HCP, and lay caregiver, and – if they include connectivity – allow reliable and timely monitoring of medication use. A digital service can facilitate many of the

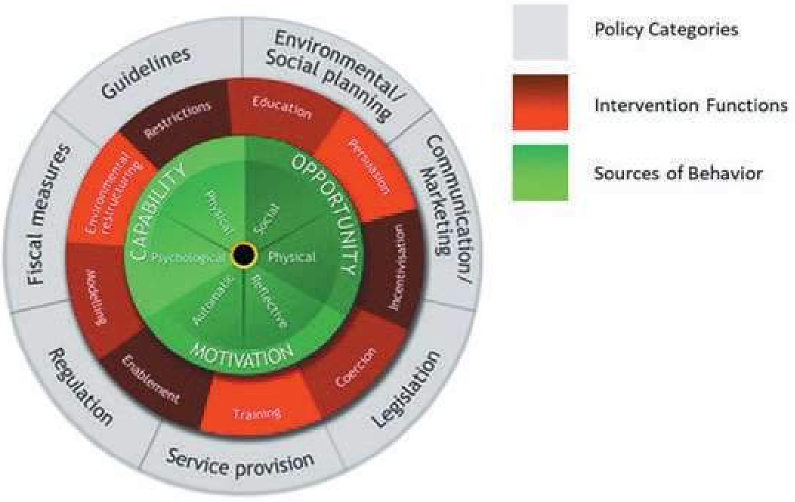

Figure 3: The Behaviour Change Wheel

behavioural change techniques described in the Behaviour Change Wheel.

Digital approaches to disease management should be backed by substantial evidence, have a reliable infrastructure, be designed collaboratively as clinically- and cost-effective systems, and reflect the needs of patients and healthcare providers. Given the challenges in supporting adherence for inhaled drugs in respiratory disease, it is not surprising that there has been increasing interest in the development of smart inhalers combined with digital services, in recent years as technology has become available.

Smart Inhalers and Connected Health

Blakey *et al*.[20] conducted a review of digital intervention used in respiratory medicine, aiming to improve adherence. Between 2007 and 2017, they identified more than 25 studies, many of which were randomised controlled studies. Although many of the studies showed improved adherence for the intervention group compared to the control group, fewer showed improved outcomes. The authors concluded that the use of digital technologies in respiratory diseases offers great potential in improving adherence, raising its importance and also supporting better inhaler technique. However, to achieve success requires a focus on the end-user to support long-term use, and to ensure uptake by HCPs, the solutions need to be better integrated into healthcare systems.

Developments around smart inhalers and digital services in respiratory diseases continue to gather pace. At this year's RDD conference, which was rather aptly presented in online format due to the COVID-19 situation, a significant part of the plan was given over to advances in inhalers, particularly around the use of connectivity – a topic that hardly merited mention 10 years earlier. Bonham *et al*. described how the addition of sensors to inhalers, connectivity and data analytics could improve inhaler use, encourage better dialogue between patients and clinicians and improve the health-related decision process, for example, to predict exacerbations. Results were presented from a study that used an add-on device (Turbu+ monitoring device developed by AstraZeneca in partnership with Adherium) with a standard Turbuhaler dry powder inhaler. The research conducted in Italy showed good adherence compared with that typically observed in the country, but was not a head-to-head controlled study.

In another paper, Chrystyn *et al*. described the ProAir Digihaler®, the first connected inhaler with integrated sensors to measure inhaler use and inspiratory flow. Inhalation information is presented on a patient app that allows the patient or their caregiver to monitor usage and identify potential inhalation errors. Data was presented that showed an accurate measurement of inhalation, and the authors anticipated that as more data is gathered from the devices in real use, this can potentially be used to develop algorithms that might predict the risk of exacerbation. The authors also recognised that more work is required to ensure digital inhalers are adopted in the market and the case for reimbursement developed. Moore presented adherence data gathered from patients using both connected maintenance and rescue therapy inhalers. There were several intervention groups ((1) access to maintenance therapy adherence data for patients only, (2) for patient and HCP, access to maintenance and rescue therapy adherence data for patients only (3), for patient and HCP) and one control group. Results showed a statistically significant increase in adherence in months 4–6 for all the intervention groups compared to the control group for the use of maintenance therapy. Overall adherence was higher

CAPABILITY	MOTIVATION	OPPORTUNITY
The individual's physical and psychological capacity to engage in the behaviour*	***All brain processes that energise and direct behaviour***	***All factors lying outside the individual that make performance of the behaviour possible or prompt it***
Psychological *Capacity to engage in necessary thought processes*	**Reflective** *Evaluations and plans*	**Physical** *Physical opportunity provided by the environment*
•Comprehension of disease and treatment •Cognitive functioning (e.g. memory, capacity for judgement, thinking) •Executive function (e.g. capacity to plan)	•Perception of illness (e.g. cause, chronic vs. acute etc.) •Beliefs about treatment (e.g. necessity, efficacy, concerns about current or future adverse events, general aversion to taking medicines) •Outcome expectancies •Self-efficacy	•Cost •Access (e.g. availability of medication) •Packaging •Physical characteristics of medicine (e.g. taste, smell, size, shape, route of administration) •Regimen complexity •Social support •HCP-patient relationship / communication
Physical *Capacity to engage in necessary physical processes*	**Automatic** *Emotions and impulses arising from associative learning and/or innate dispositions*	**Social** *Cultural milieu that dictates the way we think about things*
•Physical capability to adapt to lifestyle changes (e.g. diet or social behaviours) •Dexterity	•Stimuli or cues for action •Mood state/disorder (e.g. depression and anxiety)	•Stigma of disease, fear of disclosure •Religious/cultural beliefs

Figure 4

	Mortality	Morbidity	Healthcare utilisation	Healthcare costs	Patient satisfaction	QoL
Reminders	(4RCTs)	(5RCTs)	(2RCTs)		(2RCTs)	(2RCTs)
Simplified dosing		(2RCTs)	(2RCTs)		(2RCTs)	(3RCTs)
Direct observed treatment (DOT)	(1RCT)	(1RCT)				
Patient education	(2RCTs)	(3RCTs)	(7RCTs)	(1RCT)	(1RCT)	(8RCTs)
Counselling	(1RCT)	(2RCTs)	(1RCT)		(1RCT)	(3RCTs)
Web-based programmes			(1RCT)			
Prescribing pharmacists		(1RCT)	(1RCT)			(3RCTs)
HCP access to adherence info.		(2RCTs)	(2RCTs)			

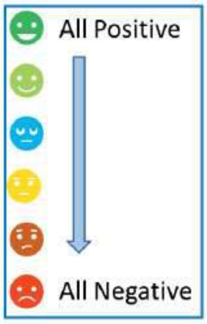

Figure 5: Summary of adherence intervention type and effects on outcomes [from Wilhelmsen and Eriksson][20]

for all groups than levels seen in routine clinical practice, highlighting the problem of the "Hawthorn Effect" when participants know they are being observed. Giving HCP access to the data (for use in an interim consultation) and access to the adherence data from the rescue medication did not seem to influence adherence. In another paper presented at the conference, Tweedie described user research to establish the minimal viable product for a connected inhaler. This research found a high level of enthusiasm for connectivity of an inhaler to an app, preference for a screen on the device to provide the necessary information, and a longer battery life. The importance of ensuring good environmental sustainability for the product was also strongly highlighted.

Discussion

There continues to be increasing interest in connected smart inhalers with more products in development likely to enter the market in the coming years. But the RDD papers discussed above also show there are challenges in realising their potential. Moore showed the difficulties of the challenges of gathering adherence data in clinical studies that are representative of the real world. Tweedie pointed out the challenges in explaining the economic value of connected devices, and Bonam stated the need to move from pilot studies to more extensive real-world studies. With the arrival of products such as Digihaler in the market, this is becoming a reality. However, it is also clear that for a good effect to be achieved, the right interventions need to be designed that can influence behaviour towards better adherence.

However, systematic reviews of interventions such as dose reminders do not provide compelling results in terms of improvement in adherence and/or clinical outcomes. Wilhelmsen and Eriksson conducted a comprehensive review of systematic reviews of medication adherence interventions and their impact on various health outcomes. Their review included data from 28,600 participants in 37 randomised controlled studies[21]. The results shown in Figure 5 show negative results for most adherence interventions against a range of outcomes. Focusing on the treatment of asthma using inhaled steroids, Normansell *et al*. performed a meta-analysis on data from 39 RCTS and a total of 16,303 participants[22]. They saw an increase in adherence for interventions targeting adherence education, electronic trackers or reminders, and simplified dosing regimens, with the former showing the most significant effect of 20 percentage points overall in the control group. However, this increase did not translate into improved outcomes for exacerbation requiring oral steroids, asthma control, unscheduled healthcare visits and quality of life. As pointed out by Moore, they noted that participation in a trial affects adherence, confounding results, and that studies would have benefited from better blinding, use of objective measures and validated questionnaires.

As pointed out by Michie *et al*., consistent application of BCTs needs to be ensured if study data is to be compared, and optimal interventions are to be designed to support adherence.

Conclusion

As more smart inhalers and associated digital services enter the market, the opportunity to gather more real-world data and test out different interventions will increase. The ability to collect an accurate timestamp of when an inhaled medication event took place and ideally, whether it was free from inhalation errors, is a significant step forward. However, if the technology is to bring real benefit in improving adherence, attention to the design of the intervention needs to be given. The work being done by Michie *et al*. to catalogue BCTs and encourage consistent application in the development of BCIs is an important step forward. Improvements to study designs, as pointed by Normansell and Moore, are also critical. But, as was the case in reducing inhaler use errors ("can use"), user research will continue to play a key role in developing an understanding of how device and app features can support "want to use". In everyday life, such as in e-shopping, we have experienced the value of good web and app design which encourage use, as well as the frustrations of poorly designed solutions that achieve the opposite.

In some cases, the technical difference between the two extremes is small, but the difference in outcomes is immense. As Michelangelo said, "Perfection is not small, but it is made up of small things". If digital interventions are to succeed in improving the adherence of inhaled drugs, such attention to detail is going to be critical.

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