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Review

Adherence in paediatric respiratory medicine: A review of the literature

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EDUCATIONAL AIMS

The reader will come to appreciate:

- Aspects of patients' reasoning for non-adherence with asthma medications.
- How adherence is measured.
- Recent developments in technology allowing more accurate measures of asthma control.
- Ways of individualising patient outcomes.
- The utility of smart-inhalers in improving asthma control.

ABSTRACT

Poor adherence is an important factor in unstable disease control and treatment failure. There are multiple ways to monitor a patient's adherence, each with their own advantages and disadvantages. The reasons for poor adherence are multi-factorial, inter-related and often difficult to target for improvement. Although practitioners can implement different methods of adherence, the ultimate aim is to improve health outcomes for the individual and the health care system. Asthma is a common airway disease, particularly diagnosed in children, often treated with inhaled corticosteroids and long-acting bronchodilators. Due to the disease's tendency for exacerbations and consequently, when severe will require unscheduled health care utilisation including hospital admissions, considerable research has been done into the effects of medication adherence on asthma control. This review discusses the difficulties in defining adherence, the reasons for and consequences of poor adherence, and the methods of recording and improving adherence in asthma patients, including an in-depth analysis of the uses of smart inhalers.

Introduction

Adherence refers to a patient's decisions on complying with healthcare advice given by professionals [1]. The World Health Organisation (WHO) describes adherence as 'the degree to which a patient's behaviour corresponds with the agreed recommendations from a healthcare provider' [2]. Although compliance, concordance and adherence are often used interchangeably, they do not have the same definitions. Compliance is defined as 'the extent to which a patient's behaviour matches the prescribers advice [3]. With these definitions in mind, compliance reflects a patient's obedience rather than adherence, which refers to a patient's deeper understanding and willingness to implement the suggested changes into their lifestyle [4]. In contrast, concordance describes the mutual agreement to a prescribed treatment plan between the medical professional and patient [5].

It is often difficult to pinpoint the exact reasons why patients may not adhere to their medication plans. However, this distinction in reasoning may be pivotal in improving health outcomes, decreasing hospital admissions and the cost burden on health care systems. It may also allow health care professionals to tailor their interventions to best improve an individual patient's adherence to treatment.

Adherence to prescribed medication is an important factor in

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determining a patient's health outcomes. Those patients whose adherence is improved through interventions tend to increase their health outcomes when compared to those with poorer adherence, as has been demonstrated using blood pressure control [6]. Although difficult, improving treatment adherence will ultimately decrease the consequences of patients' diseases.

Asthma is the most common inflammatory lung disease in children [7]. The disease has variable phenotypes and endotypes (mechanisms) [8], with eosinophilic asthma, driven by eosinophils and T helper type 2 inflammation (Th2) [9], being most common. Th2 inflammation, mediated by interleukins (IL-4, IL-5, and IL-13) causes approximately 50% of mild to moderate asthma and most of the diagnosed severe asthma. Symptoms of asthma not only affect a patient's everyday life but can be life threatening [10]. Treatment is often prophylactic, using inhaled corticosteroids (ICSs) and long-acting beta$_2$ agonists (LABAs). Patients with uncontrolled asthma may be considered for biological therapies, such as monoclonal antibodies targeting type 2 inflammation [11].

This review discusses adherence in terms of patient's reasoning for non-adherence, how adherence is measured and the recent developments in technology allowing more accurate results and how we, as medical professionals, can help improve a patient's adherence. Also discussed are the potential consequences of non-adherence with regards to asthma.

Defining adherence

Adherence has proven challenging to define. Previous studies have classified adherence into unintentional and intentional subgroups [1]. Unintentional non-adherence is due to a patient's education level, treatment complexity or forgetfulness. These reasons make modifying unintentional non-adherence much easier to remedy than intentional non-adherence. Intentional non-adherence is often due to a lack of motivation or ingrained personal beliefs about their treatment plan, often contradicting or refuting the medical professional's advice. For these reasons rectifying intentional non-adherence is much more complex, especially in the paediatric setting where a parent or carer bears responsibility for the delivery of medication to their child.

There has been a long-standing debate within the literature of what percentage definitions to use when defining good or poor adherence. It is generally accepted that adherence $\geq$ 80% is regarded as good adherence, although other definitions, such as 75%-125% [12–14] have been suggested. Poor adherence is accepted at $<$ 80% but has been split into moderate adherence of 79%-60% and poor adherence $<$ 60% [15]. In reality, non-adherence to medication for a patient with chronic disease is, on average, 50% [16] with 15% to 30% non-adherence to newly prescribed treatments [17].

Adherence has also been split into three classified domains: treatment initiation, implementation and persistence [18]. The knowledge of these domains allows practitioners to target specific areas of weakness for an individual patient or their parents. They allow the correct intervention to be employed with the aims of improving adherence and health outcomes.

The consequences of poor adherence

Poor adherence can have significant effects on the child's health outcomes. Non-adherence to asthma treatment is directly associated with decreased clinical control and greater number of acute exacerbations [19]. A randomised controlled study including General Practitioner (GP) enrolment revealed that those who had received reminders to take their medication had an adherence improvement of 73% $\pm$ 26% versus those who did not 46% $\pm$ 28% ($p < 0.0001$). This resulted in significantly improved asthma control ($p < 0.0001$), However, after adjustment for history of previous exacerbations, this result failed to reach statistical significance ($p = 0.06$) [20]. This represents adherence as having a direct impact on asthma control but may not always affect exacerbations, a key indicator of longer term asthma outcomes.

The economic impact of poor adherence is enormous. If 25% of patients who are non-adherent begin to adhere to their asthma medication, estimated calculations have shown that worldwide US$13.7 billion will be saved annually, together with avoidance of 7 million hospitalisations [21].

The ability of newer smart inhalers to measure inhaler technique as well as dose counting are likely to lead to further increase the improvements in outcomes. The CRITical Inhaler mistaKes and Asthma ControL (CRITIKAL) study, in 2017, identified which inhaler technique errors were clinically most important [22]. They noted that, with Turbohaler and Diskus devices, insufficient inspiratory effort (32%-38%) and, in metered dose inhalers, actuation before inhalation (24.9%) were linked with uncontrolled asthma. These results highlight the importance of inhaler training and technique prior to prescribing them and demonstrate an area of improvement that the new smart inhalers can target.

Measuring adherence

There are many methods of measuring adherence, both qualitatively and quantitively. However, many of them are limited by patient bias. Cost is also a factor affecting the use of more accurate adherence measuring devices, such as the Smart Inhaler (Adherium, New Zealand). Although it is possible to measure the number of doses taken by patients, including children, using many of these methods, it is important to note that there is no way of differentiating between why the patients are not adhering or whether they are taking their medication exactly as prescribed. This is particularly important in paediatric asthma as inhaler technique is pivotal in ensuring correct medication delivery.

Patient self-reporting (including dose counters)

Self-reporting is one of the most common methods of adherence monitoring. It can involve children and their parents verbally reporting the adherence or documenting adherence in a diary or questionnaire. This method is low cost and does not impact the prescriber's time [23]. Nonetheless, this method is vastly affected by patient bias. The majority of patients overestimate their adherence when self-reporting [24].

The 2019 U-BIOPRED study compared the Medication Adherence Report Scale (MARS), a form of self-reporting, and biochemical measurements of adherence, by way of measuring urinary corticosteroid levels, to determine patient adherence. They determined that 53% of patient adherence detection did not match between methods. However, the patients who self-reported better adherence had greater asthma control and better quality of life [25]. Their results put into question whether self-reporting is a worthwhile method of measuring adherence.

Some inhalers have dose counters. Dose counters were primarily designed to indicate to patients when their inhaler medication will run out. However, they can also be used to measure adherence. Again, they do not provide any information on whether the medication is being inhaled, or the date or time the medication was administered. Dose counters are difficult to interpret when used routinely and require more labour than other methods.

Prescription pick-up records

This method of measuring adherence requires prescribers to note when a patient's prescription is picked up or replenished. The prescribed amount of medication is then compared with the prescription refill records and presented as either a ratio or percentage.

The data is collected retrospectively, a great advantage, meaning that there is no impact on the patient's current health behaviours towards adherence. But this method has many limitations. Although the prescriptions may be picked up, there is no way of telling if the

treatment has been taken as prescribed (e.g. individual, specific dosage, timing).

A 2015 study used prescription records and an adherence definition of ≥ 80% drug use, to determine whether patients with 'difficult to control' asthma reached the criteria for a diagnosis of severe refractory asthma ('difficult to control asthma', good adherence and correct inhaler technique). They found 17% of their population had 'difficult to control' asthma, when in reality only 3.6% met the diagnostic criteria for severe refractory asthma when adherence was factored in [26]. This represents how poor prescription pick-up can be. Yet it does not show if the patients were not collecting their prescriptions or if the dispensaries were not recording prescription collection.

Biochemical measurements

Biochemical measurements provide more accurate evidence on whether the child is taking their medication. It compares pharmacokinetic data with the patients' responses to treatment [5]. Blood and urine measurements are simpler samples to collect which reflect biochemical measurements of adherence, but more invasive measures, such as biopsies, can be used in certain conditions.

Due to many medications having drug interactions and the varying responses, patients may have to the same medication, the measurement of adherence may be skewed. The disadvantage of biochemical measurements is their invasive nature and the need for practitioners' input. However, this method is not skewed by patient bias.

Although not currently used in routine care, recent research has determined thresholds for prednisolone and cortisol levels to allow diagnosis of poor adherence to inhaled steroids. These levels have also been linked to blood eosinophil levels and those who display good adherence also display lower levels of eosinophils when compared with non-adherent patients (0.09 (0.31) vs 0.51 (0.53) $x10^9$/L, $p < 0.001$) [27]. Those patients with better adherence had fewer disease exacerbations.

Smart inhalers and electronic monitoring

Electronic monitoring is used to assess medication adherence for many different conditions with the aim of improving health outcomes of patients. Smart inhalers were developed to permit adherence monitoring in respiratory disease, including in children.

The earliest smart inhaler (SmartMist, Aradigm Corporation, USA) was developed over 20 years ago. It was able to count administered doses, inhalation flow and volume [28]. However, due to the cost it did not establish a presence in the market. There are now many more different smart inhalers with abilities to count doses, assess inhaler technique and some link to the user's smart phone to provide reminders and records of their adherence.

The advantage of electronic monitoring is the accuracy in recording time and date of dose administration. This allows for reliable recording of adherence and has proven useful in clinical trials for adherence. The Outcomes following Tailored Education and Retraining: Studying Performance and AdherenCE feasibility (OUTERSPACE) trial used the Aerochamber Plus with Flow Vu smart inhaler to monitor patient's adherence and inhalation technique [29]. This study was used to assess the feasibility of using smart inhalers in randomised control trials (RCT) to explore the clinical benefits of better adherence in patients with asthma. They believed their use in RCTs was feasible, not only was objective monitoring possible but also continuous adherence monitoring of multiple inhalers in the community setting.

The cost of smart inhalers and electronic monitoring was the greatest concern when they were first introduced. However, smart inhalers are now generally more cost-effective. An Irish study showed that the smart inhaler intervention was below the Irish cost-effectiveness threshold of 45,000 euros/Quality Adjusted Life Year (QALY). With a possible saving of 845 euros/year/person [30]. These results suggest that, despite the additional cost of medication required with better adherence, the money saved from reduced hospital admissions and exacerbations is far greater. With the suggested cost of poor adherence to respiratory treatment being between $949 and $44,190 per person in the USA [31], any cost saving intervention would be worthwhile.

The major disadvantage of many smart inhalers is that there is no way of knowing if the patient inhaled the administered dose. This is termed as dose 'dumping'. Although, some e-modules, such as the Inhaler Compliance Assessment (INCA) e-module, attached to certain smart inhalers, measures a patient's inhalation profile [32]. This confirms a dose was primed and actually inhaled. The inhalation profile takes acoustic data, which can then be converted into inhalation flow against time data.

Modifiable factors

Non-adherence has been described as dimensional, and is not an 'all-or-nothing phenomenon' (1). In 2003, the WHO produced a report describing five interacting factors that can potentially affect a patient's adherence [33]. These factors are:

- Socioeconomic (e.g. medication expenses and social support)
- Therapy-related (e.g. treatment duration and complexity)
- Condition-related (e.g. symptom severity and relief)
- Health system-related
- Patient-related (e.g. distrust or forgetfulness)

The literature has also described the 'white coat' adherence phenomenon. This states that adherence improves both before and after an appointment with a medical professional. The first five days and last five days between appointments show adherence to be 88.3% ±17% and 86.4% ± 17% respectively. With adherence decreasing to 72.8% ± 22% in between these periods [34]. The period of improved adherence varies, with other studies describing a three day increase post medical appointment [35].

In the paediatric setting, a child's parents health beliefs can have an impact on the child's adherence to their medication. A Structural Equation Model (SEM) was constructed to explore this interaction. In a Chinese study, the SEM showed that parents' perceived severity of the disease positively impacted their child's medication adherence, with maternal opinions having far greater impact than paternal opinions [36]. The importance of explaining the disease process and medication routine to both the parents and children can significantly improve adherence.

Methods of improving adherence

Adherence can be improved with many different methods depending on the underlying reason for non-adherence. However, it is important to realise that each patient is an individual so not all methods will work for all patients.

Dose simplification

Understandably, patients with extensive and complicated medication schedules are less likely to adhere. There are many ways to simplify medication schedules:

- *Reducing dose frequency*: studies comparing three times daily dosing to once daily dosing uncovered an increase in adherent days from 22% to 41%. Similarly, when comparing once and twice daily dosing, an increase from 2% to 44% more adherent days was noted [37]. These results were consistent in asthma patients with 93.3% adherence when dosing once daily and 89.5% when dosing twice daily ($p < 0.001$) [38].

- *Using combined medications*: choosing a pill/inhaler containing multiple of the patient's prescribed medication has been shown to increase adherence. Using a combined pill has been shown to increase adherence by 5% and was preferred by 92% of patients [39]. Patient's using combined inhalers are 17% less likely to discontinue their medication than those taking multiple separate inhalers, and were 17% less likely to experience moderate-severe disease exacerbations [40].
- *Using formulations with sustained release*: in terms of asthma, using a long-acting bronchodilator (LABA) may be preferable to a short acting bronchodilator. Further research will be required in asthma to see if a difference in adherence is evident with a sustained release formula. However, research into other conditions has showed that such formulations increase adherence (3% increase with 10% more correctly dosed days that with regular release formulations) [41].

Patient education

Improving verbal and written education, specifically tailored towards a patient's specific disease, including how to self-manage, has proven very useful in improving overall adherence. Studies that tested cognitive-educational improvement methods displayed a 16.1% (95% CI 10.7–21.6%) improvement in adherence, versus 10.1% (95% CI 6.6–13.6%) in those who did not ($p = 0.04$) [42]. However, educational interventions alone have been proven to have little impact when used as the sole intervention [43].

Electronic reminders

Electronic monitoring can be paired with electronic reminders. The Study of Asthma Adherence Reminders (STAAR) study investigated whether daily electronic reminders had any impact on adherence and clinical outcomes in 6–16-year-old children. They noted adherence to be 70% in the treatment group and 49% in the controls ($p < 0.001$), with only the intervention group having reminder alarms [44]. The significant difference displays the effective nature of electronic reminders in improving adherence in children with asthma. This result was also found in adults, with patients who received electronic reminders having an adherence of 73% ± 26% compared to those who did not having 46% ± 28% adherence ($p < 0.0001$) [20].

Practitioner interventions

There are a wide range of interventions that a practitioner can implement to aid improvement in adherence. Education, communication, and assessment are key to creating good rapport, which in turn should aid adherence improvement.

Motivational interviewing identifies and focuses on patient's behaviours with the goal of motivating an improvement in health outcomes. It can be implemented in many different ways, including by telephone, individual sessions or in a group setting. Studies that reported the proportion of patients with good adherence displayed a relative risk of 1.17 between those who took part in motivational interviewing and the control group ($p < 0.01$), those who reported adherence continuously displayed a standardized mean difference of 0.70 ($p < 0.01$) [45].

Conclusion

Although medication adherence has previously been deemed as poor, many different interventions are now available to implement with the aim of improving adherence. These interventions outlined above display how simple it is to improve patient's adherence and consequently improve health outcomes including reducing mortality rates for those suffering with asthma and other respiratory diseases.

Future directions for research

- To assess low-cost and free on-line asthma management programmes that can be implemented to improve medication adherence in both high income and low-middle income settings.
- To Identify non-invasive biomarkers of asthma phenotypes and asthma medications that are scalable in the community setting to inform asthma control and thus guide adherence conversations.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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