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Review

Improving adherence in chronic airways disease: are we doing it wrongly?

Non-adherence to medicines is a significant clinical and financial burden, but successful strategies to improve it, and thus bring about significant improvements in clinical outcome, remain elusive. Many barriers exist, including a lack of awareness amongst some healthcare professionals as to the extent and impact of non-adherence and a dearth of skills to address it successfully. Patients may not appreciate that they are non-adherent, feel they cannot disclose it or underestimate its impact on their health in the short and longer term. In describing the evidence-based frameworks that identify the causal factors behind medicines taking (or not taking) behaviours, we can start to personalise interventions to enable individuals to make informed decisions about their treatments and thus overcome real and perceived barriers to adherence.

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Educational aims

- To understand the underlying principles of why a patient may or may not take medicines as agreed.
- To choose targeted interventions to support better adherence.

Adherence has been defined by the World Health Organization (WHO) as "the extent to which a person's behaviour corresponds with agreed recommendations from a health care provider" [1]. They suggest that in the developed world, medicines adherence in chronic conditions is ~50%, yet despite acknowledgement that non-adherence in healthcare is a clinically significant and financially costly burden, it has not changed substantially over the past 50 years [1, 2]. In this issue of *Breathe*, colleagues [3, 4] have eloquently described how adherence should be measured and the sequelae of poor adherence, and in this paper we complete the triumvirate of medicines adherence with suggested methods to improve it.

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Medicines non-adherence is common and associated with significant morbidity and mortality. @GrainnedAn and colleagues outline causal factors behind this behaviour and the appropriate individualised interventions available to support optimal medicines use. https://bit.ly/3ejJNTV

Unfortunately, there is no quick fix to improving adherence, rather "state-of-the-art" strategies need to target the patient, the provider, and the healthcare system [1, 5]. While higher order interventions affecting health policy, organisation and financing of care, and care quality programmes will likely play direct and indirect roles in promoting adherence [6], that is outside the scope of this paper, rather we will focus on the discussion of barriers to adherence for healthcare providers (HCP) and patients. We will describe theories from health psychology to first understand why our patients do not take their medicines as directed, then using examples of their application in clinical research, will suggest interventions to support its improvement. "Adherence" is used to describe the patients' medicines use process as a whole, but it can further delineated into three distinct domains [7]:

- initiation (starting treatment)
- execution (having initiated therapy, taking it as directed)
- persistence (maintenance of the treatment long term)

Where this differentiation is particularly pertinent, we will bring the reader's attention to which is being discussed.

Barriers to adherence: healthcare professional factors

Are my patients adherent?

To improve adherence, we must first acknowledge that non-adherence is present to a considerable degree in patients under our care, then respond appropriately to it. The misunderstanding by HCPs of non-adherence as an akratic act or "weakness of will" has been described previously in the context of people with sleep disorders [8] and helps us appreciate that non-adherence does not result from someone having the wrong values, rather that in spite of knowing the "best" course of action they may decide to do something else. It helps us understand why "educating" the patient alone is unlikely to improve adherence and that patients may be reluctant to "admit to" non-adherence, particularly when asked in a direct way. In an illustration of this, Engel *et al.* [9] found that patients were five times more likely to disclose non-adherence in response to being asked how often they missed a drug dose compared with those who were asked directly if they took their medication as they should.

Similarly, patients may deny non-adherence in favour of the socially desirable "adherent" response. A "no-blame" approach by the HCP, wherein we acknowledge that non-adherence is common and do not judge the person for it, is more likely to elicit an honest admission of non-adherence or expression of their doubts and concerns regarding treatment [10]. We should remember that addressing non-adherence is not about getting patients to take more medicines *per se*, rather it is the process of identifying an inability to take the treatment, exploring the reasoning for them wanting to take the therapy or not, and in bringing this together, helping the individual make informed decisions for their own benefit.

Clinicians may consider detection of non-adherence to be beyond their professional remit, ask questions that elicit a defensive reaction from the patient, or simply avoid the issue as they do not have the skills or the time to manage it [11]. A US study by Meddings *et al.* [12] investigated physician assessment of patient adherence to blood pressure medicines compared with prescription refill records. They found that doctors in the study failed to recognise non-adherence in more than half of patients, but more startlingly, they often increased antihypertensive medications even when they suspected non-adherence. Indeed, the recent Organisation for Economic Cooperation and Development (OECD) working paper included their concerns regarding clinicians being unaware of the extent and impact of the adherence problem in their patients [13].

The phenomenon of underestimating non-adherence is not restricted to physicians. A study by Clyne *et al.* [14] investigated the views of over 3000 HCPs (including physicians, nurses and pharmacists) who provided care to adults in a primary care setting in 10 European countries. It aimed to assess their perception of patient adherence across all three adherence domains: initiation, execution and persistence at 1 year. HCPs were asked to answer questions on two distinct populations with a chronic illness: "patients in their country" generally and "their own patients" specifically. Interestingly, they found that participant's perceptions of medicines adherence differed significantly when considering their own patients in comparison to general patients. HCPs perceived their patients to be more likely to initiate therapy, less likely to adhere to the regimen and more likely to demonstrate persistence after 1 year. The authors hypothesised as to the potential reasons for these differences (including HCPs preferentially looking to confirm suspected good adherence, rather than seek poor adherence), and concluded that an unconscious optimistic bias among HCPs was likely to create an overestimate of medication adherence.

This tendency to overestimate medicines adherence in one's own patients is likely caused by a number of factors but reflects another common issue in decision making: sampling bias. That is, adherence may be higher in patients who attend appointments and, not surprisingly, clinicians base their judgements on these patients rather than those who have stayed away [14]. Whatever the reason for this inaccuracy, if clinicians are not

aware of the extent of the adherence problem, they will be unlikely to routinely enquire about adherence and even less likely to offer adherence support.

How good is good enough?

We know that medicines not taken appropriately are unlikely to have the desired effect, but in considering the need to improve adherence, another difficulty arises: what level of adherence are we hoping to achieve? Ideally, targets should be derived from clinical evidence, based on optimal outcomes and minimal adverse effects. In 2000, Paterson *et al.* [15] robustly described the case for protease inhibitor therapy adherence needing to be ≥95% for patients with HIV infection to optimise virological outcome. Similarly, in the seminal clinical trials investigating tuberculosis management, the assignment of "adequate adherence" was defined as 76%–80% of intended doses taken [16, 17] and allowed appropriate comparison and assessment of response. Interestingly, such was the strength of influence of non-adherence on outcome (for the patient and in avoiding resistance), that it has been suggested that clinical trials should examine more than one threshold for non-adherence (*e.g.* 80% and 95%) to more robustly assess efficacy [18]. When describing adherence to continuous positive airway pressure (CPAP) two figures are considered: the number of hours of CPAP use per night and the number of nights that this target is achieved. While Kribbs *et al.* [19] may have arbitrarily defined optimal CPAP adherence as at least 4 h of CPAP administered on 70% of days monitored, this has been accepted as the standard target and adherence interventions explored to reach it [20]. This pragmatism and consistency of approach has unfortunately not been adopted in airways diseases, and as yet, no such threshold has been universally agreed for inhaled therapy use. This is a seemingly frustrating failing, but as we move towards more clinically appropriate biomarker-led care, perhaps we should not request a one-size-fits-all figure, rather a more accessible way to achieve the individualised maximal response/minimal adverse effect level of inhaler use [21, 22]. The effects of such a strategy in the run-in phase of a clinical trial would be particularly interesting.

Barriers to adherence: patient factors

Patients may be non-adherent for many reasons, and these can vary between individuals and in the same individual over time. However, in better understanding the underlying causes, we can employ strategies to militate against them. Broadly speaking, adherence can be classified as unintentional or intentional. Unintentional non-adherence is considered a passive process whereby patients do not take their medicines due to circumstances outside their control (*e.g.* forgetfulness, not understanding the instructions or an inability to pay for therapy). Whereas intentional non-adherence is defined as an active decision by the individual to not take treatment (thought to be driven by patient beliefs about their treatment, disease and prognosis, as well as their objective experiences with medications). While traditionally it was felt that unintentional non-adherence was driven by demographic characteristics (*e.g.* younger age, female gender), in truth, patients may exhibit both types concurrently, one can lead to the other, and the boundaries between the two may not be as distinct as previously considered. For example, someone is less likely to forget a medicine they perceive to be essential than one considered unimportant [23].

Airways disease is predominantly managed by inhaled therapies (categorised as pressurised metered dose inhalers (pMDI) or dry powder inhalers (DPI)) and this mode of delivery adds a unique complexity to achieving optimal adherence. It is estimated that as many as 80% of people with asthma are unable to use their prescribed device correctly [24, 25], with similar figures reported in COPD [26]. Poor inhaler technique is considered "unintentional", but unfortunately it is not clear how clinicians can most effectively intervene to improve it [27–29] and the interventions needed to improve the technique of people with asthma appear different to those necessary for those with COPD [26, 30]. Cushen *et al.* [31] described the adherence of patients with COPD as one of four inhaler use clusters: 1) regular use/good technique, 2) regular use/poor technique, 3) irregular use/good technique and 4) irregular use/poor technique. They found that not only were patient outcomes different depending on their "cluster" but reinforced the idea that the interventions to increase adherence should also be different. In a final twist, in isolation the inhaler technique observed with either type of device may be satisfactory, but the co-prescribing of a DPI and a pMDI adversely affects patient ability to use either type of inhaler optimally with resultant impacts on clinical outcomes in COPD [32], and asthma in both children [33] and adults [34]. This suggests that it is crucial not only to check and improve inhaler technique, but where possible rationalise multiple prescriptions to one device or the other.

In focusing attention on detecting non-adherence, we have rather neglected what we should do when we find it. To date, most research on interventions to promote adherence has been by health psychologists and focused largely on understanding and then attempting to modify patient behaviour. Several theoretical models have been developed to explain and try to predict adherence to prescribed treatment. They

encompass patients' beliefs about health, their beliefs about illness and the treatment prescribed, but increasingly, more comprehensive frameworks recognise that medicines taking behaviour is multifaceted and must incorporate assessment of a wide variety of factors. Indeed, the WHO suggested that the most promising methods to support adherence use a combination of strategies tackling patient education, behavioural skills, self-rewards, social support and telephone follow-up [1]. Hence by believing that health behaviours are modifiable, the hope is that in understanding the types and causes of non-adherence, one can tailor interventions to address them.

The earliest approaches for understanding and improving adherence were based on attempts to provide better information and improve recall [35]. The assumption was that communication about treatment with patients was often limited and/or of poor quality, so patients did not understand what they were required to do and subsequently forgot. Since then, from the large number of studies investigating reasons for non-adherence, a wide range of possible factors have been identified. These have been incorporated into a framework [36], which identifies three broad groups of causal factors and proposes that people need the capability (C), opportunity (O) and motivation (M) to perform a particular behaviour (B) (COM-B). COM-B has been applied to a number of health contexts including treatment adherence [37] and this is outlined below.

Capability is the patient's psychological and physical ability to engage in a behaviour. When applied to treatment adherence, psychological ability can include the patient's capacity to understand, remember and plan to take their treatment, whereas physical ability may refer to the level of dexterity required to use a device, such as an inhaler. While better communication and understanding can improve adherence to a degree for patients in whom this is their main adherence barrier, there is clear evidence that providing reminders does not really help people who have already become non-adherent [38].

Opportunity covers the physical and social factors external to the individual that make the behaviour possible or prompt it. Physical factors include ease of access to the healthcare system, financial constraints, the complexity of the regimen, and even the taste of the medicine itself. Social opportunity factors include the quality of support from healthcare providers and from family and friends, who can encourage or discourage medicines taking, and the wider social context (*e.g.* religious or cultural beliefs held by the patient). Interventions involving support from HCPs have been shown to improve adherence, but unless these strategies improve motivation, they are unlikely to be successful [39].

Motivation is the want or need to perform the behaviour in the context of competing demands at that moment. It is a key driving force for engaging (or not) in any health-related behaviour, including treatment adherence. There are two broad groups of motivational factors: reflective and automatic. Reflective factors include the patient's beliefs about medicines (*e.g.* the perceived need to use the treatment as prescribed, the anticipated or experienced negative impact of side-effects) and the condition being treated (*e.g.* the patient's beliefs about the perceived seriousness or controllability of their condition). Where a clinician has not set realistic expectations for the patient with respect to a treatments potential benefits, onset of action or side-effects, it is logical that if a patient takes their medicines as advised initially, then experiences adverse effects or indeed, no effect, that they then decide not to take further doses. The failure here is in that decision not being communicated to the clinician. Automatic motivational factors include the patient's mood, their habits and other decision-making heuristics. Medicines taking may have been incorporated into daily activities, for example medicines are taken with breakfast or associated with setting their alarm clock in the evening; however, when the routine is disrupted the cue to action may be missed resulting in the medicines not being taken.

All three groups of factors in COM-B are important to ensure a behaviour will be carried out, but at an individual patient level, it is crucial to identify their key barrier(s) in order to support or change their adherence behaviour. To do this, the HCP will need to ask open-ended questions to uncover the factors responsible for that person's adherence problems. This can be supplemented or facilitated by using simple screening questionnaires, which allow the patient to indicate their main adherence challenges. A recent example of this is the brief pre-consultation screener: "Making medicines work for you" [40]. It consists of a simple checklist where the patient indicates whether they are experiencing any of seven problems with their medicines, rather than asking them directly about their adherence. It is drawn from the COM-B framework, so includes items which assess capability (I cannot manage so many medicines), opportunity (I cannot afford either the time or money to get the medicines) and motivation (I am not sure if the medicine is really helping me). A pilot study among patients with diabetes found that the screener could identify a range of medicines-related issues and that 88% of the sample indicated at least one issue, contrasting with the relatively small numbers who typically disclose non-adherence verbally [40]. Table 1 provides examples of the COM-B framework applied to respiratory medicine.

COM-B is not the only framework to support adherence in practice. The Perceptions and Practicalities Approach (PAPA) [11] also aims to support the understanding of medicines taking behaviours and offer practitioners a suite of multi-layered pragmatic interventions that can be tailored

Table 1 *Capability, opportunity and motivation to perform a behaviour (COM-B) [37] model applied to patients with respiratory disease and suggested solutions*

Barrier	Potential solution
Capability (patient factors)	
Psychological ability	
Does not understand treatments	Ensure your patient understands the purpose of their medicines
Forgets to take medicines	Use reminder apps or an alarm on their phone
Does not have a plan to take their treatment	Facilitate implementation intention: work with the patient to help them identify ways that medicines taking could be associated with their established daily activities (*e.g.* tooth brushing)
Physical ability	
Poor dexterity	Issue an inhaler device they can readily use or equipment to facilitate its use
Opportunity (external to patient)	
Physical factors	
Restricted access to healthcare system	Encourage regular review (even when well), provide emergency access to care and advice
Financial constraints	Provide information on pre-payment or exemption certificates, prescribe several inhalers at once in systems that charge per prescription (rather than per item)
Complex regimen	Simplify regimens where possible
Dislike of the taste of the medicine	Change to an alternative brand, formulation or delivery device (*e.g.* some patients distinctly prefer a DPI or pMDI)
Social factors	
Lack of support from healthcare providers	Be supportive and non-judgemental
Lack of social circle support	Engage family members, friends or other patients for support and encouragement
Religious/cultural beliefs	This may lead to rejection of an inhaler containing alcohol, so offer a DPI or an inhaler brand without alcohol
Motivation	
Reflective factors	
Patient's beliefs about medicines/ about their condition	Support understanding of the disease as present even in the absence of symptoms, and how the use of the chosen medicine treats the disease Describe the benefits of the therapy in terms of short-, medium- and longer-term benefits Acknowledge the potential for side-effects, and contextualise their risk of experiencing them, how to manage them or how long they may persist; this may need to be in comparison to previously tried therapies Reassure the patient that, if necessary, alternatives exist
Automatic factors	
Patient mood	Addressing low self-esteem, depression and anxiety will support better adherence
Habit	Change incongruent regimens to suit the patient's lifestyle/preference (*e.g.* if evening doses are regularly forgotten, suggest the dose be taken in the morning)

to an individual. It is based on the premise that two key and inextricably linked factors are essential for adherence: motivation and ability. It considers the patient's decision-making process (predominantly by exploring their beliefs around disease, treatment necessities and concerns) and marries that with the practicalities of taking therapy as directed. Its underlying message is that when practical barriers are removed, adherence only occurs when the value of a particular therapy overcomes the person's concerns about taking it. This is a necessity and concerns model, where necessity beliefs (effectively answering the question "why do I need to follow this treatment to achieve my aim", and more subtly "how much of this can I get away with not taking?") are evaluated alongside concerns.

Concerns encompass side-effects (those anticipated or experienced previously), the disruptive effects of taking a medicine on daily life (for example it being an unwelcome daily reminder of the presence of disease) and often the misconception that taking treatments regularly may lead to dependence, accumulation (and therefore adverse effects) or that efficacy will diminish over time.

An interesting and relatable factor described by Horne *et al.* [11, 41], is that of a patient's perception of "sensitivity" to the effects of medicines, with many believing themselves to be more sensitive than others. This could manifest itself as them being more prone to side-effects or as needing less treatment to derive the beneficial effect. In this case, the patient's strategy of non-adherence may be to minimise harm to themselves. To address these necessities, concerns and practicalities, PAPA reinforces the need for a no-blame approach to empower patients to discuss non-adherence openly and honestly. While conceptual framework models form the basis of interventions, in practice, do they deliver improvements in adherence and does this improvement positively affect clinical outcome?

Interventions tested for impact on adherence

A Cochrane systematic review spanning several chronic diseases identified the following factors as having a positive influence on adherence: using simpler dosing regimens, having pharmacist involvement in care, provision of reminders/cues, education delivered with self-management training, and to a lesser degree, financial incentives [42]. The benefits of a systematic approach to improving overall lung health and medicines adherence by HCPs in general have been described elsewhere [43, 44], as have the data to support specific pharmacist-delivered interventions in asthma [45–47] and those emerging in COPD [48–51]. The studies described below focus on evaluating the interventions themselves rather than who provided them.

Asthma education and self-management

Apter *et al.* [52] aimed to test the impact on adherence and outcomes associated with standard asthma education (SAE) *versus* an individualised, four-step problem-solving technique (including: identifying specific barriers to adherence, brainstorming solutions with the patient, appraising the options together to choose the best solution, and then subsequent amendment of the intervention based on its impact). A sample of 333 adults with moderate or severe persistent asthma were recruited from low-income urban neighbourhoods and were both reimbursed for participation and supplied the inhaled corticosteroid (ICS) free of charge. Patients were randomised to participate in four 30-min sessions of community based standard asthma education or individualised problem solving over 3 months, and then followed up for a further 3 months. Adherence was monitored electronically. The overall mean adherence was "relatively good" at 61±27%, although it declined over the study period by 14% in the usual care group and 10% in the intervention group. In spite of this decline, there was a statistically significant improvement for both groups in the six-item asthma control questionnaire (ACQ6) [53], quality of life (AQLQ) [54], and percentage predicted forced expiratory volume in 1 s, but no difference in emergency department attendances or hospitalisations. The investigators concluded that problem-solving does not improve adherence or decrease asthma morbidity; however, it may be that the benefit of such an intervention was lost within them addressing a primary (opportunity) barrier to adherence, treatment affordability, and it may also reflect that the "standard" asthma education addressed crucial capability barriers.

A randomised controlled trial by Christakis *et al.* [55] aimed to test whether an interactive website that prompted parents to assess their child's asthma and gave tailored feedback and advice on adherence strategies could improve self-reported ICS adherence for children with asthma. 603 eligible patients (29% classified as having mild to severe persistent asthma, 71% mild intermittent asthma) were randomised to the intervention monthly for 6 months, while the control group completed a non-asthma related questionnaire at the same frequency. Both groups received vouchers for participation for the first 6 months, and were then offered an optional additional non-incentivised 6 months. Overall, 85% of parents completed the 6-month assessment and 80% completed the full year, suggesting that the incentive was not a key driver of participation for either group. Interestingly, the intervention had no impact when considering patients who were not using a controller therapy at baseline but should have been (non-initiators). However, in patients who were already using a controller medicine at baseline, the intervention group had greater adherence at 6 months, but this did not persist, so there was no discernible difference between groups at 12 months. There were no differences in asthma-related quality of life measures between groups at either time-point. The reasonable conclusion was that a tailored interactive website could increase ICS adherence, but only during the period of active intervention, and that this change was not associated with improvements in patient-reported quality of life.

Janson *et al.* [56] conducted a randomised prospective trial of 84 patients with moderate-severe persistent asthma who were recruited from private and public community clinics. They investigated the impact on ICS adherence and asthma control of "usual care" *versus* a programme of three 30-min, individualised, self-management face-to-face education sessions that included: asthma information, inhaler technique optimisation, agreement of an action plan and trigger avoidance strategies with support to self-monitor symptoms and peak flow. These consultations were delivered bi-weekly over 4 weeks, with follow-up observation for a further 14 weeks. ICS adherence was measured electronically and categorised as ≥60% or <60% adherence to prescribed doses. Participants were reimbursed for their time and received their ICS free-of-charge. The 45 participants who were randomised to receive the self-management intervention maintained a consistently higher ICS adherence level than the control group. Interestingly, the effect was more pronounced at the end of the 4-week intervention period, a nine-fold increase in the odds of ≥60% adherence compared with control, compared with threefold greater odds at the end of the study. This improvement also affected outcomes, including improvement in perceived control of asthma, decreased night-time awakenings and decreased inhaled β_2-agonist use, but also highlights the relatively limited impact of a discrete intervention on promoting persistence with treatment.

Reminders

Non-initiation or primary medication non-adherence (PMN) is defined as patients not picking up a first prescription. Fischer *et al.* [57] investigated whether a telephone call intervention from the physician's office to patients who had not picked up new prescriptions after three phone calls from the pharmacy, would have an effect. Patients receiving new prescriptions for medications treating asthma, hypertension, diabetes or hyperlipidaemia were identified, and as part of an existing programme received two automated and one live call from the pharmacy encouraging them to pick up their prescription. Those who cancelled their prescriptions or had not picked them up after the third pharmacy call were eligible for this study. 148 patients were randomised to no further follow-up and 142 to the intervention group, which received a telephone call from a nurse to assess reasons for PMN and encourage pickup of prescriptions. Up to three attempts were made to reach each patient by the nurse. Initial PMN rates in the overall population were lower than similar studies at 6%, and the intervention did not change subsequent collection rates: 25% of intervention patients, 24% control patients. This suggests that the pharmacist's initial efforts were effective, confirms that additional similar reminders will not increase collection further and that the residual PMN was unlikely to be because the patient had forgotten.

Julious *et al.* [58] recognised that the return to school in September was associated with a peak in asthma episodes in school-aged children and postulated that this was linked to the observed fall in prescription collection in August. They therefore investigated the impact of writing to parents/carers in August reminding them of the importance of medication taking and ensuring sufficient treatment supply prior to returning to school. In August, the proportion of children who collected prescriptions increased (odds ratio 1.43), as did scheduled contacts (OR: 1.13); however, in September the proportion of children who had an unscheduled medical contact increased (OR: 1.09). The reasons for the apparent lack of translation into a September benefit were unclear.

A study by Foster *et al.* [59] investigated the change in ICS/long-acting β-agonist (LABA) adherence (monitored electronically) of 143 patients with moderate-severe asthma. The interventions were: general practitioner (GP)-delivered usual care, GP-delivered personalised adherence discussion (PAD), and an inhaler reminder (provided if doses were missed) with adherence feedback (IRF). Patients were randomised to receive usual care, PAD, IRF, or IRF plus PAD and the effect on asthma control was measured using the Asthma Control Test (ACT) [60]. After 6 months, adherence was significantly higher in the IRF group than in non-IRF groups (73±26% *versus* 46±28% of prescribed daily doses; $p<0.0001$), but not between PAD and non-PAD groups. Asthma control improved overall (mean change in ACT score 4.5±4.9; $p<0.0001$), but there was no significant difference among groups. The authors concluded that inhaler reminders may improve patients adherence in primary care compared with a behavioural intervention or usual care alone, but that this may not translate into an improvement in asthma control.

Adapting services

Following the implementation of a four-phase asthma management programme in Quebec province, Canada, Guénette *et al.* [61] evaluated the "integrated care" intervention (described as "a process to ensure that services provided by HCPs from different organisations are mapped and linked to the particular needs of each individual") *versus* "usual care". Patients aged 12–45 years were recruited from pharmacies, with 108 patients participating in the programme and 241 not exposed to it. Asthma control was measured using the ACQ5 (score ≥1.5 indicates inadequately controlled asthma) [62], and ICS adherence was assessed using the Morisky medication adherence scale (MMAS-4) [63] and the medication possession ratio (MPR) [64]. At baseline, the proportion of

participants with "good" ICS adherence (MMAS-4 of zero or MPR ≥75%) was low in both groups: 15.8% and 9.1%, respectively. After 12 months, only the exposed participants showed an improvement in adherence measured by MMAS-4 and by MPR, however, asthma control improved significantly within both groups (no significant difference seen between groups). This result may be because all participants received an asthma action plan and peak flow meter at recruitment, but also because participation in the programme was reported as low. The authors concluded that an integrated intervention, with HCPs collaborating to optimise asthma control can improve ICS adherence, but correctly pointed out that although statistically significant, the actual improvements for individuals were modest, and thus, did not translate into better asthma control.

The devastating effect of undertreated tuberculosis and therefore the need to guarantee adherence in some patient groups through directly observed therapy, has been recognised for over 20 years [65]. In a similar type of intervention, Harrington *et al.* [66] investigated the administration of ICS doses to 46 disadvantaged school children with asthma over a 60-day period. The intervention group (n=19) had the morning ICS dose administered by the school nurse, with other doses given by the parent as usual, while the control group had all doses administered by the parent. Adherence was calculated from nurse- and parent-reported doses administered. Children in the intervention group received 91.7% of expected morning doses of ICS (some doses missed due to school absences), but interestingly, there was no significant difference between groups for number of morning doses or evening doses taken. Despite this, the intervention group reported significantly less functional limitation, better adjustment to family life, and less parent sleep loss than control patients at the end of the study period. This methodology probably facilitated an overestimation of home administration, but the usefulness of the strategy is more limited by an inability to sustain this intervention long term or apply on a larger scale and the lack of longer term support for patients/parents to take ownership of adherence, a particular problem for older children and young adults [67–71].

Electronic adherence monitoring and feedback

It seems logical that novel studies using an objective assessment of adherence (*e.g.* an electronic inhaler device) *versus* traditional measures (self-reported adherence or prescription collection information), would deliver more accurate results. Sulaiman *et al.* [72] recognised that in difficult-to-treat asthma, poor control could reflect suboptimal medication adherence (infrequent dose administration and/or poor inhaler technique), or genuinely severe refractory asthma. They tested their hypothesis that regular visual "(bio)feedback" to the patient on their specific adherence components would improve adherence, by recruiting patients under a hospital clinic with uncontrolled asthma to receive intensive education (including repeated training in inhaler use, adherence and disease management), with or without (bio)feedback. The primary outcome was inhaler adherence, and the secondary outcomes included clinical outcomes (assessed using peak expiratory flow, ACT and AQLQ). The mean rate of adherence during the third (final) month in the (bio) feedback group (n=111) was significantly higher than that in the group receiving intensive education alone (n=107; 73% *versus* 63%), although both rates were higher than previous similar studies, which the authors attributed to the effectiveness of their intensive education programme. At the end of the study, asthma was stable or improved in 54 patients (38%); uncontrolled, with adherence <80% in 52 (35%); and uncontrolled, but adherence >80% in 40 (27%). Thus, the results of this study suggest that (bio)feedback of adherence and intensive education are superior to intensive education alone in supporting persistence with medicines, and facilitates clinicians identifying patients as refractory or in need of further adherence support.

These results are in contrast to a recent study by Moore *et al.* [73] investigating the effect a clip-on inhaler sensor, a patient-facing app and HCP dashboard. They found that despite a statistically significant increase in ICS adherence of 12% in the Ellipta-monitored arm, there was no significant difference between groups after 6 months using the ACT score [74]. Whether this reflects a flaw in the ACT as a measure of clinical outcome, that the cohort were sufficiently adherent at the beginning of the study that this absolute increase (equivalent to one additional dose of maintenance medication per week) was unlikely to bring about a readily detectable improvement, or something else, is unclear. It is, however, important that we do not lose faith in the benefit of incremental adherence improvements in individual patients, or underestimate the impact of these devices for facilitating conversations about adherence between clinicians and patients and potentially improving inhaler technique through real-time feedback.

In summary, these studies suggest that adherence may improve with individualised self-management education programmes, by feeding back on inhaler deviations and by providing free prescriptions to those who would otherwise pay, but there is limited evidence to support interventions reminding patients (or their parents) to collect or administer medication, for redesigned services that patients do not engage with or that usurp

patient/parent responsibility in medicines use. The waning adherence seen over even short periods of time suggests that interventions require regular refreshing to maintain impact [52, 55, 56, 73].

Limitations of improvements in adherence

Somewhat surprisingly, common themes in adherence are that its improvement does not consistently result in a corresponding improvement in biomarkers, morbidity, mortality, quality of life, patient satisfaction, healthcare use, or costs [73, 75–78], that symptoms do not beget adherence [79] and the effectiveness of seemingly similar treatments may be affected differently by concomitant treatment adherence [80, 81]. A 2017 Cochrane review aimed to assess the efficacy and safety of interventions intended to improve adherence to ICS therapy in asthma [75]. It found that while the pooled results of studies suggested that some interventions could improve adherence, the relevance of this improvement for an individual was less clear. It concluded that this lack of translation of an increase in adherence into better clinical outcomes was most likely due to methodological limitations (including inconsistent measurement of an intervention or objective impact), that in several studies adherence improved in the control and intervention arm, so not really comparing an intervention with "usual care", and the significant risk of bias from inclusion in an adherence trial. The significant risk of bias is that a non-adherent person would be unlikely to agree to participate and the potential for a "Hawthorne effect" (also referred to as the observer effect), where individuals modify or improve an aspect of their behaviour in response to their awareness of being observed. There would appear to be limited capacity to remove this bias from adherence studies, but having a long duration of follow-up may mitigate its influence on results.

At this point, a note of care is required regarding the unintended consequences of the sudden onset adherence, as seen in a study published in the *BMJ* in 2005 [82]. In this study, investigators aimed to determine the effect of a home-based medication review by pharmacists (that included supporting better adherence) on hospital readmission rates among older people. It found that the intervention was associated with a significantly higher rate of admissions and lead to a cautionary speculative message from the authors was that this "counterintuitive" finding may have been due to an improvement in adherence leading to iatrogenic adverse effects.

In conclusion, we should assume that a degree of non-adherence is present in all of our patients at some time, learn to investigate the reasons behind this without judgement and engage the patient in application of relevant and individualised interventions to improve and maintain adherence. We should appraise the potential risk (current and future) that non-adherence presents to the patient, and be able to discuss this in a way the person can understand. In lieu of wider acceptance in respiratory medicine of brief interventions to address non-adherence (in a similar way as for alcohol and smoking), it follows that HCPs need to develop their own simple, practical and generalisable process, and to regularly review whether the success of the interventions in the short and longer term to maximise clinical outcomes.

Self-evaluation questions

1. During your consultation with a person with poorly controlled asthma, she tells you that she doesn't use her ICS as she is concerned that it will cause weight gain. Should you:
   a) Change her ICS therapy to a once daily preparation.
   b) Stop the ICS and consider other therapeutic options.
   c) Reassure her that an ICS will not cause side-effects (*e.g.* weight gain).
   d) Discuss the relative risks and benefits of steroid therapy (oral and inhaled) on management of her asthma.
2. A person with well controlled COPD tells you he sometimes forgets to take his evening medicines. Should you:
   a) Change his inhaled therapy to a once daily preparation to take in the morning.
   b) Offer him a pharmacy-filled monitored dosage system (*e.g.* a dosette box).
   c) Suggest he set a reminder on his phone and incorporate evening doses into his dinner time or bedtime routine.
   d) Acknowledge how difficult it is to remember and reassure him that as he is well controlled currently, it isn't a problem.
3. A gentleman with asthma tells you that he doesn't use his ICS/LABA inhaler as he cannot afford to pay for it and his short-acting β-agonist. Should you:
   a) Suggest that he purchase a pre-payment certificate to allow all prescription items to be free.
   b) Recommend a ICS/LABA "maintenance and reliever" regimen.
   c) Ask the primary care provider to issue several inhalers on each prescription.
   d) Any of the above depending on the individual circumstances.
4. A person tells you that they never miss doses and use their preventer inhalers "religiously"; however, their primary care prescription record suggests that they have only collected salbutamol in the past 6 months. Should you:
   a) Tell them that you know this isn't true and show them the prescription record.
   b) Refer them to the pharmacist (or other suitably trained healthcare professional) to improve their adherence.
   c) Follow them up sooner than planned to re-discuss medicines use.
   d) b and c.

Key points

- While the extent of suboptimal adherence in chronic respiratory disease and its significant deleterious impact on morbidity and mortality is acknowledged, to date, little has had a significant impact on improving it in practice.
- Clinicians underestimate the extent of non-adherence in their patients and, if they do enquire about adherence in consultations, often do so in ways which make patients unwilling to disclose it.
- There is a paucity of evidence supporting the utility of large-scale interventions to improve long-term adherence, but understanding the reasoning behind non-adherence may help clinicians implement interventions to better support it for an individual.
- Given the tendency to lapse into non-adherent behaviours, adherence should be considered a chronic concern in need of long-term monitoring and on-going support.

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Suggested answers

1. d.
2. Potentially a or c, depending on patient preference.
3. d.
4. d.

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