# Interventions to improve adherence in children with asthma: A systematic review

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October 5, 2021

**Abstract**

Introduction: Non-adherence to inhaled corticosteroids (ICS) in children with asthma leads to significant morbidity and mortality. Few interventions to improve adherence have been effective and little is known about what contributes to intervention effectiveness. This systematic review summarises the efficacy of these interventions and the characteristics of effective interventions to inform future studies aiming to improve adherence to ICS in children with asthma. Methods: PubMed, Embase, PsychINFO, Medline, Web of Science, and International Pharmaceutical Abstracts were systematically searched on the 3rd of October 2020 for randomised control trials measuring adherence to ICS in children with asthma. A narrative synthesis was conducted focusing on intervention efficacy and study reliability. Intervention content was coded based on the NICE guidelines for medicines adherence (The Perceptions and Practicalities Approach, PAPA) and Behaviour Change Techniques (BCT), to determine the effective aspects of the intervention. Results: Of 240 studies identified, 25 were eligible for inclusion. Thirteen of the twenty-five studies were categorised as being highly reliable. Nine of the thirteen studies were effective at increasing adherence and six of those met the criteria for a PAPA intervention. Conclusion: Adherence interventions in children with asthma have mixed effectiveness. Effective studies tended to be of higher quality, were tailored to individuals perceptual and practical adherence barriers, and used multiple BCTs. However, due to the small number of included studies and varying study design quality, conclusions drawn here are preliminary. Future research is needed to test a PAPA-based intervention with a rigorous study design as outlined in this review

## Interventions to improve adherence in children with asthma:

## A systematic review

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**Take home message:** Interventions to increase adherence to ICS can be effective in children with asthma, but more rigorous intervention methods are needed. Patients' beliefs about ICS and their ability to adhere should be targeted in future patient-tailored interventions.

**Key words:** Adherence; diagnosis; asthma; intervention; inhaled corticosteroids; systematic review

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Methods: PubMed, Embase, PsychINFO, Medline, Web of Science, and International Pharmaceutical Abstracts were systematically searched on the 3rd of October 2020 for randomised control trials measuring adherence to ICS in children with asthma. A narrative synthesis was conducted focusing on intervention efficacy and study reliability. Intervention content was coded based on the NICE guidelines for medicines adherence (The Perceptions and Practicalities Approach, PAPA) and Behaviour Change Techniques (BCT), to determine the effective aspects of the intervention.

Results: Of 240 studies identified, 25 were eligible for inclusion. Thirteen of the twenty-five studies were categorised as being highly reliable. Nine of the thirteen studies were effective at increasing adherence and six of those met the criteria for a PAPA intervention.

Conclusion: Adherence interventions in children with asthma have mixed effectiveness. Effective studies tended to be of higher quality, were tailored to individuals perceptual and practical adherence barriers, and used multiple BCTs. However, due to the small number of included studies and varying study design quality, conclusions drawn here are preliminary. Future research is needed to test a PAPA-based intervention with a rigorous study design as outlined in this review.

# Introduction

Asthma is the most common chronic non-communicable disease in children worldwide [1]. Asthma prevalence is higher in children in Europe (8.9%), compared to the rest of the world (7.2%)[2] but varies between countries [3]. Most children with asthma achieve good disease control with maintenance low dose inhaled corticosteroids (ICS), which are effective at preventing most asthma hospitalisations and deaths [4]. However, some children remain poorly controlled despite being prescribed high-dose ICS treatment, often due to poor adherence. This contributes to suboptimal asthma control and severe attacks[5; 6]. Up to half of patients attending tertiary care paediatric asthma clinics are non-adherent (defined as taking less than 80% of their prescribed dose)[7].

The Global Initiate for Asthma (GINA) highlights that suboptimal use of asthma treatment is a patient-specific barrier that contributes to the burden of asthma [8]. Similarly, the UK National Review of Asthma Deaths reported that 67% of asthma deaths were avoidable, and one of the most important avoidable factors was low ICS adherence in the month and/or year before death [9].

Many interventions have been developed to address the issue of poor ICS adherence in children. A meta-analysis in adults and children identified that interventions for improving adherence in asthma can be

effective[10]. However, the meta-analysis did not examine the intervention characteristics e.g. content, channel of delivery and context of the intervention, which form the three components of behaviour change framework (3CBC[11]) in relation to intervention efficacy. It is important to be able to identify characteristics of effective interventions so that they may be applied in practice.

Moreover, the reliability of the diagnosis of asthma and the adherence measurement tool have not previously been used to identify high reliability interventions. If patients are diagnosed with asthma incorrectly, non-adherence to a treatment that is therefore unnecessary is logical. Similarly, if adherence is overestimated in studies using unreliable adherence measurements, then the conclusions drawn from the studies will also be inaccurate. By investigating these factors, the data presented in this review are likely to be more relevant to practice as they represent a rigorous test of the intervention.

The National Institute for Clinical Excellence (NICE) has developed guidelines intended to aid the design of adherence support for long term conditions at any stage of the life span [12]. The guidelines apply the Perceptions and Practicalities Approach (PAPA[13] E-image 1). This approach recognises that adherence varies within the individual, over time and across treatments. Adherence/non-adherence is best understood in terms of the interaction between an individual and a particular treatment. It is a variable behaviour rather than a trait characteristic. The Perceptions and Practicalities Approach (PAPA) conceptualises adherence as including both intentional and unintentional non-adherence.

The application of the PAPA approach to adherence interventions has the following key features firstly, the need for a no-blame approach as patients are often reluctant to admit to non-adherence, or to concerns about the treatment, as they fear that this may be interpreted by the clinician as doubting their expertise. Hence, non-adherence and the reasons for it are often hidden. The second key feature is the need to tailor support to address both *perceptions* (e.g. beliefs about asthma and its treatment) and *practicalities* (e.g. clear instructions on inhaler technique, establishing a medication routine). Both perceptions and practicalities influence the patient's motivation and ability to start and continue taking the treatment. Indeed, research in asthma has shown beliefs about ICS are often important perceptual barriers to adherence, particularly doubts about the personal need for regular inhaler use particularly in the absence of symptoms and concerns about corticosteroids [14; 15].

This systematic review aims to address these research gaps by 1. Specifically examining adherence in children with asthma 2. Using quality indicators to identify those studies that may be more informative, and3. Examining the characteristics of adherence interventions to identify features that may be relevant to practice.

# Methods

## Search Strategy

PubMed, Embase, PsychINFO, Medline, Web of Science, and International Pharmaceutical Abstracts databases were searched systematically from the date of database inception until 3rd October 2020 to identify relevant literature. MeSH, Emtree and truncated terms were used where applicable (E-table 1). Key search terms were: asthma, child, Intervention, adherence and randomized. All authors were contacted via email or, if not reachable via this route, by ResearchGate messaging for further details about the studies.

### Study selection

Authors CP and TJ reviewed the abstracts, followed by the full texts against the inclusion/exclusion criteria. Where there were differing opinions a third, opinion was sought (RH). Inclusion criteria were based on the Participant-Intervention-Comparison-Outcome-Study Design (PICOS) framework. Any interventions that focused on adherence to ICS with at least one outcome measure of adherence and used a randomised control trial (RCT) design were included. The comparison group was either usual treatment or basic education

arms. Articles were included where the full text was written in English, and where the population of interest was patients aged 0-18 years old with a diagnosis of asthma. Although many preschool children with wheeze do not respond to ICS[16], studies often recruit younger children and therefore this age-range was intended to avoid missing relevant articles. If they do not have the treatable trait of airway eosinophilia likely to respond to ICS [17] this will be highlighted in the section regarding reliability of the criteria for asthma diagnosis. Studies were excluded if they did not meet the above criteria or if they were an RCT comparing two medications only, or where the majority of participants were not children (e.g. the mean age of participants was over 18 years or only adults were recruited).

**Data Extraction and Synthesis**

Following full-text review, CP and TJ extracted details of: study characteristics (setting, number of participants, diagnosis criteria, intervention and control descriptions and the outcome of interest); Effectiveness; Risk of Bias (RoB); and Behaviour change techniques (BCTs); target of the BCTs; relationship to PAPA.

Intervention Content

Intervention content were coded for PAPA as follows: Level 1 (intervention only targeted perceptions or only practicalities and not tailored); Level 2 (both perceptions and practicalities targeted but not tailored or only targeting one component (perceptions or practicalities) and tailored) and Level 3 (both perceptions and practicalities targeted and tailored to the individual).

Specific components within the intervention for changing adherence (Behaviour Change Techniques; BCTs) were also coded independently using BCT taxonomy V1 app [18]. Any differences in the selected BCTs were discussed until consensus was reached (Table 1).

Risk of Bias

RoB was assessed independently using the Cochrane Risk of Bias Handbook[19] by CP, AC and HF using the Covidence platform (*www.covidence.org*) to record coding decisions and consensus discussions. The RoB score was based on the adherence outcome. Each study was scored across five domains: selection bias; performance and detection bias, attrition bias and reporting bias, and was scored as either low, high or unclear risk for each study. Authors were contacted for clarity when information relating to domains seemed unclear.

Study Reliability

To ascertain which interventions were truly effective, study reliability was considered. Although other validated tools have been used to assess quality such as the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) tool [20] the authors felt that there were several crossovers between risk of bias, the reliability scores, the 3CBC approach and in particular, the indirectness section of the GRADE tool and based on the aim of this review the reliability measurements would be more useful when considered with RoB. Both diagnosis and adherence measures can range from being subjective to objective, therefore considering the reliability of the approaches used is key for determining study reliability. Through multidisciplinary team discussions (including with respiratory physicians, pharmacists and a health psychologist) a coding hierarchy that considered the reliability of the asthma diagnosis and adherence measurement used was created and applied to the specific studies within this review (E-table 2).

Based on the RoB, the reliability of the asthma diagnosis, and the objectivity of the adherence measurement, the most reliable and least biased studies were used to ascertain what components constituted an effective intervention. Previous literature suggests that optimising the context, channel of delivery, and content of the intervention is important for intervention effectiveness [11], and thus the 3CBC [11] was also applied to this review.

Studies were summarised by a narrative synthesis. Meta-analysis was not conducted due to the wide study heterogeneity in terms of setting, asthma diagnosis criteria, and outcome measures used. The

study protocol is published on PROSPERO (*https://www.crd.york.ac.uk/prospero/#searchadvanced*) (ref: CRD42016029213).

# Results

## Search Results

The literature search retrieved 255 articles. An additional nine were identified from other sources. Twenty-two duplicate articles were removed before abstract screening. Based on abstract screening, 202 papers were excluded and a further 13 papers were excluded based on the full text. Main reasons for exclusion were: study design not an RCT; no usual care control group; medication adherence not included as a usable outcome; trial compared medications or was conducted in adults. Twenty-five studies were included in the narrative synthesis[21-45]; see full PRISMA diagram (Figure 1).

Figure 1: PRISMA flow diagram showing study selection

## Narrative Synthesis

### Study characteristics

Effect on adherence

Less than half of the interventions (44%, 11/25) showed significant improvement in adherence in the intervention groups compared to the control groups [23-25; 32-34; 36-38; 41; 44] (Table 2).

### Study Reliability

Although half of the studies were reported as effective at increasing adherence the study reliability varied widely (Table 3). A wide range of criteria were used for the diagnosis of asthma and therefore the patient sample included in each study was heterogeneous. Where reported, most diagnoses were based on guidelines such as GINA, National Heart, Lung, and Blood Institute (NHLBI) [24; 25; 35] or a physician diagnosis plus a prescription for ICS [23; 26; 28-30; 37] (50%, 9/18). Just under half (44%, 8/18) reported using an asthma diagnosis given by the emergency department physician[21; 32; 38] , where patients asthma symptoms will have been directly observed by physicians, or by diagnosis from medical records [22; 27; 31; 34; 36]. Asthma diagnosis criteria was generally poorly reported.

Based on the coding hierarchy which considers the reliability of the asthma diagnosis (E-table 2), seven studies used reliable means to diagnose asthma in their participants [21; 23; 24; 32; 36-38]. Three studies used less reliable methods [25; 34; 35] and a further seven used unreliable diagnostic methods[22; 26-31]. In one study the method of diagnosis of asthma was unclear [33].

Adherence measurement varied with studies using objective and subjective measures. Based on our coding hierarchy of objectivity of adherence measurements (E-table 2), most studies used more objective measurements[23; 24; 28; 31; 33; 34; 36; 37] or both objective and subjective measures [26; 27; 35]. Six used subjective measurements of adherence only [21; 22; 25; 30; 32; 38]and for one study, the method of adherence measurement was unclear[29]. Based on the RoB, reliability of asthma diagnosis and objectivity of the adherence measurement within each study the reliability of the evidence can be summarised (Table 3).

### Risk of Bias

Risk of bias within studies

Nearly one third of the studies were considered low risk[21; 23; 24; 34; 38; 39; 41; 43] , with most (n=10) being considered moderate risk [22; 26; 30; 32; 33; 35-37; 40; 44]. Six studies were considered high risk[25; 27-29; 31; 42] (Table 3 and Figure 2).

Figure 2: Risk of Bias within and across studies

Risk of bias across studies

The main bias identified was performance bias. Overall, RoB was low for most studies in terms of selection bias (random sequence generation); detection bias (blinding of outcome assessment) and reporting bias (selective reporting bias). Section bias (allocation concealment) was often low or unclear and was generally poorly reported. Attrition bias (incomplete outcome data) was frequently unclear or high risk (Figure 2).

### Reliability of the evidence

The most reliable studies (i.e. moderate or high reliability based on asthma diagnosis and adherence measurement criteria) and low/ moderate RoB are discussed in more detail below. Nine of the thirteen studies in this category were effective at increasing adherence[23; 24; 32-34; 36-38; 41] and four were ineffective[21; 26; 35; 39]. The following section compares the nine effective studies with the four ineffective studies within this high reliability group. Of those studies which reported effectiveness for increasing adherence, only one study was not considered to be in the high reliability group.

Components of effective interventions

This section will summarise the findings of this systematic review based on the 3CBC framework [11] in order to critically appraise the effectiveness of the components within the most reliable intervention study evidence.

### Context

The eight effective studies were conducted in Brazil[24]; Greece [41];New Zealand[23; 32]; China[44]; the USA[38]; the UK [34; 36]; and the Netherlands [37]. The ineffective studies were conducted in the USA [21; 26; 28; 31; 39; 42], Taiwan[35], Brazil[45], the Netherlands[40] and Sweden[43; 46]. Effective studies took place in an emergency care setting [23; 38]; primary care [24; 34]; hospital outpatients[33; 36; 37; 41; 44]; and in the community[32; 44]. The ineffective studies took place in: emergency care [21; 39], in the community[26; 40], primary care[42; 43] and in hospital outpatients [35; 43; 45].

There are no data regarding whether or not the interventions used a no-blame approach [11] but three of the high reliability effective studies were clearly tailored to the patient[24; 32; 33; 41] compared with only one of the ineffective studies [35].

### Channel of Delivery

Seven of the high reliability effective studies used technology to deliver the intervention including using electronic monitoring devices (EMDs [23; 33; 36; 37; 41]), the telephone[24], a patient and health-care provider app[44] and a SMS-based system [37]. Seven of the ineffective studies used technology to deliver the intervention via an educational video[42], website and monthly telephone calls [26], SMS text reminder and tips (not personalised) [39], a smartphone app[40; 43] and via the internet alone[35]. Different health care practitioners were involved in the interventions. Effective studies involved Pharmacists[23; 37], nurses [23; 24; 32; 33; 36; 41; 44], specialist physicians [32; 33; 36-38; 44], community health workers [32] and researchers[37]. In one study (1/8), the only channel was a letter sent from the patients' GP [34] to the parents of the child with asthma. The ineffective studies used limited contact with any health care practitioner [21], pharmacist[40],nurse [26; 35; 42; 45] and physician [35; 42; 43].

### Content

Summary of perceptions and practicalities targeted by adherence interventions

Of the nine effective and highly reliable studies, six met the criteria for Level 3 (67%; [24; 32; 33; 36; 38; 41] (Table 4). The three other effective and high reliability studies were categorised as Level 1 or Level 2 with one untailored intervention focusing practical and perceptual factors[34], one focusing only on practical factors [23] and one targeting practicalities in a tailored way [37]. Of the highly reliable studies only four were not effective- two were categorised as Level 3 [26; 35], one was categorised as Level 2[39] and one was categorised as Level 1[21].

Only two effective studies were classified as low reliability and categorised as Level 3 [25; 44]. The ineffective and low reliability studies were either classed as Level 1 (no tailoring)[27; 42; 43], Level 2 perceptual only[29; 30], or both but not tailored [22]or Level 3 [28; 31; 40; 45]. Therefore, only six studies using Level 3 PAPA were not effective (6/25, 24%), four of which were classed as low reliability studies. Overall, only 18% (2/11) of high reliability studies using Level 3 of the PAPA did not result in effective studies.

Summary of Behaviour Change Techniques used

The most commonly used Behaviour Change techniques within effective and highly reliable study interventions were: Non-specific rewards[33]; Prompts/cues [23; 24; 33; 34; 36; 37; 39; 41; 44]; Feedback and Monitoring [23; 33; 36-38]; Pharmacological support (this often involved providing free medications in countries where medications were not free and providing a longer-term supply when the medications were free) [23; 24; 33; 34; 38]; Instruction on how to perform a behaviour[32; 33; 36; 38; 41] and Information about antecedents[32; 41]. Relevant to the age of the participants, the BCTs most often targeted both parent and child with the aim (primary or secondary outcome) of improving the child's adherence to ICS. Only in one instance did the BCT pharmacological support target only the parent in the form of a letter to encourage the parent to pick-up the child's ICS prescription [34]. Four further studies specified that the interventions targeted the child specifically[23] and these were often with older children[24; 28; 29]. For extracted examples of common behaviour change technique and the studies they were used in see Table 5. For full details of the behaviour change technique extraction for each included study see Table 1.

# Discussion

## Summary of the Evidence

This is the first review to summarise effective interventions to increase adherence in children with asthma, taking into account the reliability of the studies and the behaviour change framework and techniques used in a clinically meaningful way. Previous reviews of adherence interventions in adults and children have shown that only half of interventions are effective at increasing adherence[10]. Similarly, we found that only nearly half of the included studies (11/25) were effective at significantly increasing adherence [23-25; 32-34; 36-38; 41; 44]. We then explored the crucial factors for an effective intervention to increase adherence.

Of the thirteen studies that were effective, nine were considered highly reliably [23; 24; 32-34; 36-38; 41]. By comparing the effective and reliable studies (9/25) (accurate asthma diagnosis, objective adherence measure and low/moderate RoB) to the unreliable or ineffective studies this review should inform the development of future interventions. In terms of context high reliability interventions carried out in the UK (2/25) and New Zealand (2/25) were most likely to be effective. High reliability Interventions carried out in the USA were most often ineffective (6/25 versus 1/25 that was effective). However, regarding healthcare context there were no differences between different healthcare settings such as primary or secondary care. Three of the four high reliability but ineffective studies were not tailored to the patient group [21; 39; 47]. This highlights the importance of tailoring as it has been well reported that tailoring is associated with more effective interventions [12].

The findings of this review support the use of technology as a channel to deliver the adherence intervention including electronic monitoring devices for measuring adherence and patient and health-care provider apps and telephone calls. Healthcare practitioner type is not as important as face-to-face contact while providing

digital interventions. This finding supports a previous recent review based on digital interventions in long-term conditions [48]. Those planning an adherence intervention should therefore consider the amount of contact alongside digital interventions as a key component to future effectiveness.

In terms of content, six out of the nine reliable effective interventions were coded as Level 3 PAPA [24; 32; 33; 36; 38; 41]. Three high reliability and effective studies did not meet the criteria for Level 3 PAPA [23; 34; 37]. Overall, only two of the highly reliable studies based on Level 3 PAPA did not result in effective interventions [26; 35]. The two studies had moderate risk of bias and did not involved face-to-face contact with a healthcare professional.

PAPA is easy to apply when developing an intervention as it simply highlights the effective minimal ingredients for change in adherence[49]. This review found that currently developed interventions in this area largely neglect the role played by patient beliefs about asthma and ICS. Research shows that these are often important determinants of non-adherence in adults[50; 51] and there is immerging evidence of relevance in children [52]: in terms of parental [53; 54] and adolescent beliefs [14; 15]. Patient's perceptions that are of particular importance are beliefs about their personal need for treatment (even in the absence of symptoms) and concerns about steroid safety. These issues are important because necessity and concern beliefs may be the drivers of adherence as they influence motivation to adhere to treatment [55; 56].

The most common BCTs used in effective interventions were prompts/cues (e.g. reminders), feedback and monitoring; pharmacological support and instruction of how to perform a behaviour. Each BCT was found to be most effective as part of complex interventions when tailored to the patient. It is currently unknown how many and what combination of BCTs are likely to increase the effectiveness of an intervention. However, this review is the first to show that particular BCTs are important to consider when developing a tailored intervention for increasing adherence in children with asthma.

**Strengths and Limitations**

Due to the heterogeneity of the adherence outcomes, limited availability of raw data and a small number of eligible studies a meta-analysis was not possible within this review.

This systematic review focuses on adherence as an outcome as opposed to clinical health outcomes as unlike within the adult literature, few studies in paediatric asthma include both adherence and clinical outcomes. Focusing on adherence therefore allowed a greater number of studies to be synthesised. Ideally intervention studies should have an objective reliable clinical outcome as well as an adherence outcome to account for potential patient manipulation of the adherence measurement and for those patients that may have low adherence despite good control (likely over-medicated). However, unlike in some other conditions, adherence to ICS has been shown to be highly correlated with objective clinical outcomes [57] and therefore the use of adherence as a primary focus for this review is a reasonable proxy.

Most of the interventions had a moderate RoB which was increased by the high level of performance bias which is common in behavioural interventions. This is due to the lack of ability to blind patients and personnel to the purpose of the study, however, many of the studies tried to counteract that using deception (where ethically permitted). This included objective electronic monitoring devices also for control groups and additional measurements to distract from the adherence data collection. The studies often had low selection bias (for random sequence generation); detection bias and reporting bias; However, attrition bias and allocation concealment was frequently unclear with modern recommended reporting guidelines such as CONSORT[58] not being followed. We recommend using objective methods of measuring adherence and also more than one method of measurement, and also for the diagnosis of asthma, alongside blinding to increase the reliability of future intervention findings.

One further limitation is not excluding interventions where the diagnosis of asthma reported was not rigorous, for example where primary care medical records were used to identify those with asthma despite no record of prescribing ICS or where a physician diagnosis was given without objective measurement of asthma[59]. Future intervention studies should ensure the children recruited have a reliable diagnosis of asthma and objective

measurements of adherence so the true effectiveness of the interventions can be determined[60]. Therefore, this review considered the reliability of the evidence for both the diagnosis of asthma, the measurement of adherence and the risk of bias of the studies.

## Conclusions

Adherence interventions in children with asthma have mixed effectiveness. Effective studies tended to be of higher quality, targeted both perceptual and practical adherence barriers in a tailored manner, and used a combination of BCTs. However, due to the small number of included studies and varying study design quality, conclusions drawn here are preliminary.

None of the studies have explicitly addressed ICS necessity and concern beliefs. This remains a potential area of investigation as a method for enhancing adherence. Future interventions could consider a closer use of the NICE guidelines including addressing patient's beliefs and the channel by which the intervention is delivered; the increasing use of EMD with feedback delivered in a no-blame collaborative consultation. Future research is needed to test a PAPA-based intervention with a rigorous study design as outlined in this review.

# Funding

Funding by the Asthma UK Centre for Applied Research via a PhD studentship. RH is also funded by NIHR CLAHRC North Thames. AB is an NIHR Senior Investigator emeritus. LF is an Asthma UK Senior Clinical Fellow.

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