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Review Article

Technological and digital innovations in improving adherence to asthma medication therapy

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Abstract

This article aims to explore the technological and digital innovations developed with the purpose of advancing adherence in asthma patients. The focus is on the inhalers and their digital innovations as well as fully digital adherence-supporting technologies.

A literature search in the PubMed database was performed. Out of 184 identified studies, 39 articles were left for the analysis.

All technological improvements are nowadays registered as electronic medical devices. Technological improvements are connected with the inhaler and target the inhalation technique and performance. The influence on adherence is made through recording doses, improving medication delivery through proper inhalation, measuring the date and time of medicine administration, etc. Fully digital innovations provide more opportunities to improve patients' adherence through the possibility to directly influence therapy, build databases with treatment outcomes, engage psychologically and emotionally, consult virtually, etc.

Technological and digital improvements in asthma medication adherence provide innovative options to improve the therapy.

Keywords

digital health, asthma, adherence, literature review, health technologies

Introduction

Asthma continues to be a significant chronic disease burden, with estimated patient numbers approaching 350 million globally. It could lead to a serious decline in lung function, frequent work absences, and long-term complications (Gruffydd-Jones et al. 2019). Asthma is a major source of direct and indirect economic cost in addition to reduced quality of life and premature death in patients of all ages, including children (Cisternas et al. 2003).

Adherence to medication is a major problem in asthma management, being difficult to assess and tackle (Engelkes et al. 2015). Patients' compliance with inhalation therapy is a challenge both for clinicians and patients themselves due to a difficulty in inhaling active ingredients, irregular intake of medicines, etc. (Bourbeau et al. 2008). Some authors consider that successful asthma therapy is 10% medication and 90% education (Fink 2005). When long-term therapy is in question, the average adherence rate is 50% for respiratory diseases in developed nations (Bidwal 2017).

Poor adherence leads to significant morbidity in the form of poor asthma control, hospitalisations, days out of work, and death. Many studies have highlighted the importance of high medication adherence in asthma (Zhang et al.

2023). Part of the challenge of non-adherence is the difficulty involved in measuring adherence accurately and reliably. A range of methods are available to assess adherence directly (e.g., through direct observation of medication taking or blood level tests) or indirectly (e.g., via prescription or refill records, self-report, or electronic monitoring devices). However, all these methods have their own advantages and disadvantages and can be subject to error (Vik et al. 2004).

Inhalers are improving continuously, but with the advancement of digital technologies, lots of new innovations appear in the area of patients' adherence improvement (Rafi et al. 2022). Digital technologies, such as web and mobile platforms, electronic adherence devices, etc., support diagnostics, education, stimulation and reminding, telemedicine, mHealth, etc., and have been used increasingly as part of adherence interventions. Widespread use of smartphones and tablet computers provides a great opportunity for their use in the delivery of adherence interventions (Kardas et al. 2022).

This article aims to explore the technological and digital innovations developed with the purpose of advancing adherence in asthma patients. We focus on the inhalers and their digital innovations as well as fully digital adherence-supporting technologies.

Methodology

We performed a literature search in the PubMed database. PubMed was used because it systematises publications from medical journals. Our primary focus was on medical articles exploring the technological and/or digital innovations aimed at improving adherence of asthma patients.

PubMed was searched during June–September 2024. The database was searched electronically using the following keywords: digital, asthma, and adherence.

Two researchers searched the selected abstracts and retrieved the full-text articles in case of agreement.

Review articles and interventional studies were included. Studies encompass the period 2014–September 2024. Only articles available in the English language were included. Reference lists of previously published articles were also searched to ensure complete retrieval of all relevant studies.

Excluded articles do not focus on asthma therapy, do not report clinical improvement, do not have protocols for observational or clinical studies, do not focus on adherence, or do not include technological and/or digital components.

In total, 184 abstracts were identified, and out of them, 132 were excluded. Full texts of 51 articles were left, but after the second revision, 12 full texts were excluded, and at the end, 39 articles were left for the analysis. The PRISMA flow diagram shows the search process (Page et al. 2020) (Fig. 1).

Results

Of the selected articles, 13 were reviews, either literature, systematic, or mini-reviews, and the rest, 26, were interventional or observational studies. From the interventional studies, six were for the paediatric population, three paediatric and adolescent, and the rest for adults. 14 explored technological improvements with digital components and 25 only digital interventions (Annex 1).

Technological advancements with digital components

Digital inhaler devices are among the first innovations in the area of asthma adherence improvement (Chan et al. 2021). Digital inhalers have existed for over two decades, but with the advancement of digitalisation, they started to be modernised with many digital components. The digital inhaler device can be registered and connected to a smartphone and cloud platform. Their inhaler is digitalised with electromechanical sensor(s), connected with microelectronics to detect the time and date of inhaler actuations. Connection with the clinician is through the portal to review the transmitted dashboard data. Inhalers store information about the time and date of inhalation and can guide proper inhalation effort by patients to improve technique.

Other inhalers can measure air flow during inhalation or report adequate shaking of the pressurised metered dose inhalers prior to patient use; measure inspiratory flow rate; or observe declines in lung function during exacerbations (Levy et al. 2024).

Digital inhalers allow patients to interact with them by receiving daily reminder alerts, viewing current environmental conditions, recording their health status by answering the Asthma Control Test (ACT), and reviewing their inhaler use on a daily, weekly, or monthly basis. Digital inhalers can capture objective information about inhalation events (Levy et al. 2024). Digital inhalers have the potential to 'identify' different phenotypes of asthma patients using a combination of inhaler use patterns and inhalation parameters. Thus, inhalers support earlier detection of inhalation errors and early warning signs to predict exacerbations. Analysis of these patterns also provides additional information about long-term asthma outcomes. This may help identify markers of uncontrolled disease, like, for example, frequent reliever medication use (Mehta 2021).

There are many types of digital inhalers described in the literature (Mehta 2021). Some are accompanied by primary digital platforms that improve pulmonary care. The others are an acoustic sensing device (Bosnic-Anticevich et al. 2023). Some inhalers were specially developed for the treatment or prevention of bronchospasm with reversible obstructive airway disease in paediatric patients (Dramburg et al. 2021). Self-monitoring inhalers allows patients to observe that they have inhaled all the formulation as the capsule is transparent. Bluetooth connectivity is also available to quickly store and share the inhaler usage data and evaluate adherence to therapy in children with pulmonary complications (Hui et al. 2022). Other inhalers provide an opportunity for a multi-dose inhalation and deliver several drugs for the treatment of pulmonary ailments (Molimard et al. 2021).

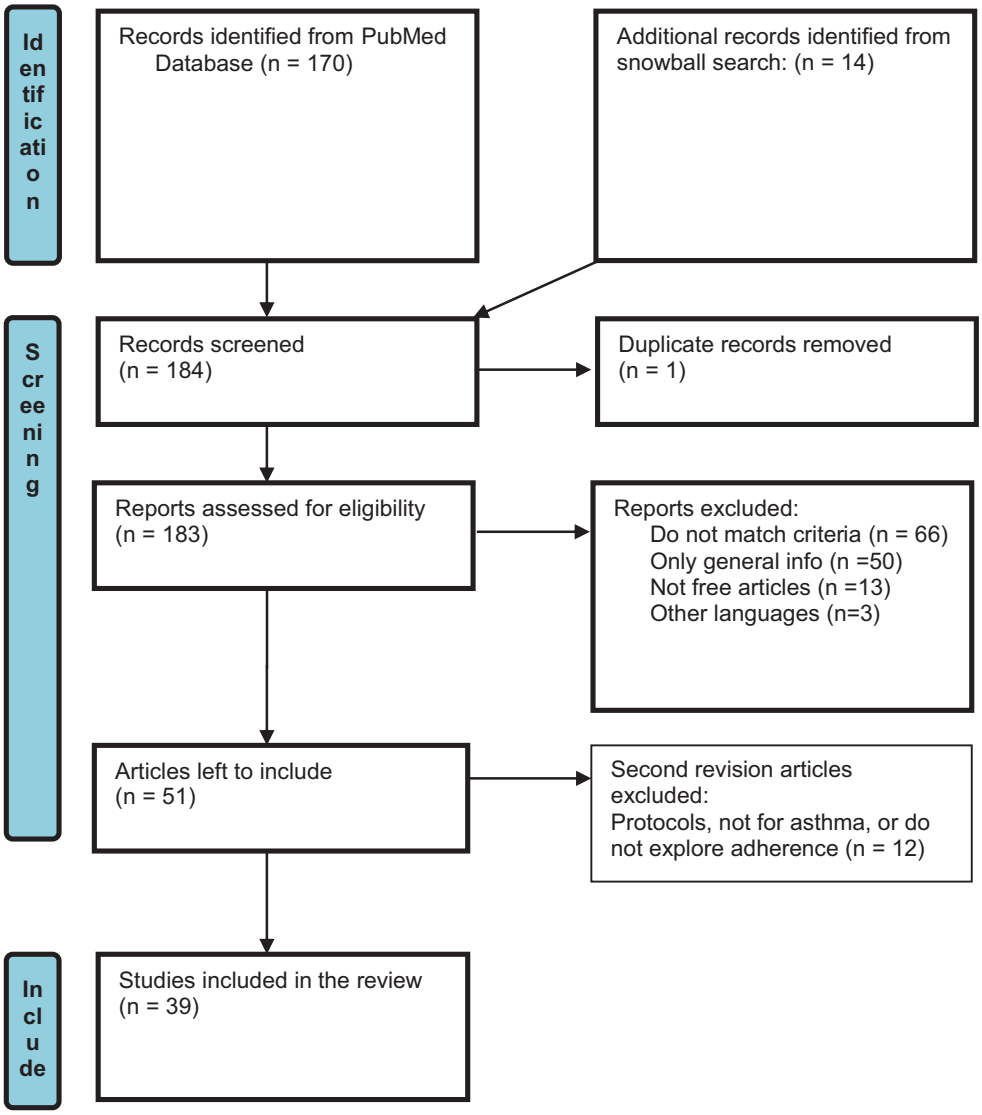

Figure 1. PRISMA diagram of search.

When the digital inhaler is synchronised with a smartphone connected to the internet, clinicians can access all data generated by these devices for each enrolled patient. (B Sousa-Pinto et al. 2023). One of the most important innovations is when artificial intelligence is added to systematise data for medication intake and to predict and/or mitigate future exacerbations. When data from different sources are gathered in one database, the exacerbation's prediction will increase its validity.

The other review article is focusing on the smart inhalers' evolution (Jansen et al. 2021). Smart inhalers have been developed from tracking devices only counting the usage of an inhaler to more sophisticated tools that can be used in different aspects of the medication adherence. In addition, options were added to inform patients about the environmental triggers (e.g., allergens and pollution) causing asthma attacks. Smart inhalers can be used to detect non-adherence, provide reminders, provide educational and motivational feedback, and improve inhaler technique. Smart inhalers are positively accepted because they make patients responsible for their therapy, provide adherence feedback, and are relatively low-priced. Negative aspects of their usage are the incompatibility with other electronic systems for data storage and brief personalised adherence discussions (PADs) techniques (Foster et al. 2014). This inhaler device contained a phone chip and an external aerial, and it automatically uploaded data to a secure website on a monthly basis. Patients can customise the ringtone and remind time. The authors consider that such an approach offers a simple, feasible, and highly effective strategy for improving the adherence of outpatients with asthma. This successful combination of reminder and feedback allowed patients to receive prompts for missed doses. If physicians revise records, they will advise patients on improving medication adherence and asthma control (Alwashmi et al. 2021).

Video directly observed therapy (VDOT) is the next innovation discussed in the studies. It invites patients to take a video when they take their medications and submit videos to their physicians (McCrossan et al. 2022). The videos are stored in a secure repository, and physicians are reviewing and providing feedback to patients. Some

VDOT platforms allow direct care from a medical team (www.continga.co.uk) or from other trained professionals (https://www.scene.health/). In addition to the tight control on patient adherence, VDOT can be used for patients with difficult-to-treat asthma (DTA).

A similar approach is used in smart spacers (Dierick et al. 2022). Smart spacers provide inhaler education and monitor with a sensor for adherence and inhalation technique. Output is assessed by reading the memory card from the smart spacer. Videos can help educate people with low health literacy (Faber et al. 2023). An animation video describes the concept and scenarios, preparing paper-based visual prototypes to facilitate the discussion with healthcare professionals.

In summary, all technological improvements are nowadays registered as electronic medical devices. They are connected with the inhaler and targeted the inhalation technique and performance. The influence on adherence is made through recording doses, improving medication delivery through proper inhalation, measuring the date and time of medicine administration, tracking the GPS location of doses, transmitting data to healthcare specialists, recording the sounds of inhalation, providing feedback from healthcare professionals, predicting triggers of asthma exacerbations, etc. A summary of advancements with digital components and their influence on adherence is presented in Table 1.

Digital technologies

Digital technologies include all technologies that are fully delivered via online (web-based) platforms or by computer programs. Within this group, we include online platforms, computer-based platforms, mobile apps, short-message interventions, computer games and programs, interactive voice response systems, telemonitoring, etc. (Chan et al. 2022).

Online platforms include websites, online forums for the provision of health information, the exchange of data, and monitoring asthma state (Milne-Ives et al. 2021). The Virtual Asthma Clinic connects physicians and patients when asthma control is low and contributes to adherence improvement. Another group of platforms is personalised health applications (MyMediHealth), which help patients to take appropriate medication and remind them. My Asthma Portal is also a platform individualised for medication control. "AsthmaVillage" is an online community for patients with asthma. Other platforms are "Living Well with Asthma", Health Village, and My Breathing Matters, which are designed websites with programs evaluating asthma control, supporting optimal medication management, assessing asthma severity and quality of life, and helping for personal action plans (Blakey et al. 2018; Ainsworth et al. 2019; Genberg et al. 2023). Platforms like

Table 1. Groups of technological advancement with digital components.

Group	Examples	Adherence influence
Digital inhaler devices	Propeller Health—global	Detect the time and date of inhaler actuations.
	Digihaler	If connected with a smartphone, a mobile application can interact with the patient.
	Amiko Respiro	Connect with the clinician.
	Adherium Hailie	Store information about the time and date of inhalation.
		Measure air flow during inhalation.
		Report adequate shaking of the pressurised metered dose inhaler.
		Observe declines in lung function during exacerbations.
		Ensure daily reminder alerts.
		Capture objective information about inhalation events, inhaler parameters, and patterns of medication use.
		Support earlier detection of inhalation errors and early warning signs to predict exacerbations.
		Systematise data for medication intake (AI-supported).
		Predict and/or mitigate future exacerbations (AI-supported).
Smart inhalers	Nebuliser Chronolog	Counting the usage of an inhaler.
	Aerosol Actuation Counter Doser (MDI)	Provide information about environmental triggers.
	Smart Mist	Detect non-adherence.
	MDILog (MDI)	Provide reminders.
	SmartTouch for Symbicort	Provide educational and motivational feedback.
	SmartInhaler Tracker (pMDI)	
	Electronic Breezhaler (DPI)	
Personalised audiovisual inhaler reminders and feedback (IRF) and brief personalised adherence discussions (PADs) techniques	SmartTrack device (Nexus 6)	Provide signals for missed doses.
		Review medication taking patterns
		Feedback with physicians.
Video directly observed therapy (VDOT)	www.continga.co.uk	Directly observed therapy.
	https://www.scene.health/	Store videos in a secure repository.
		Physicians can review and provide feedback.
		Ensure optimal inhaler technique and adherence.
Smart spacers	pressurised metered dose inhalers (pMDI) in combination with spacers	Provide inhaler education and monitor.

Smart Asthma, FindAir, MiBand3, and Mobistudy are also used to predict asthma attacks (Tsang et al. 2022). AsthmaTuner is a novel self-management cloud computing-based system (Android or iOS) (Ljungberg et al. 2019). It is created for the patients to enable self-monitoring of asthma symptoms and lung function. The storage of clinical data on platforms enables the exchange of experiences among doctors, promotes health literacy, and encourages responsible behaviour among patients.

Online communities have also focused on chronic respiratory diseases (Himes et al. 2016). The Asthma and Allergy Foundation of America, in partnership with Inspire, an online patient engagement platform, offers a website (http://www.inspire.com/groups/living-with-ashtma/) where patients can connect and provide support to one another via online discussions and educational resources. Another online community is the AsthmaCommunityNetwork (http://www.asthmacommunitynetwork.org). It provides educational resources to improve asthma care and forums for discussion between patients and health care professionals. The Chronic Obstructive Pulmonary Disease (COPD) Foundation (http://www.copdfoundation.org) has created an integrated patient and physician registry called COPD360 that includes information about asthmatic patients too. This registry gathers data from patients to identify new asthma and COPD treatments (Kohlbrenner et al. 2022).

Computer-based platforms are not necessarily connected to the internet but can record information and patient data. They could be custom-built with a home-monitoring system for long-term respiratory disease management. During the time, programs and tools were developed, such as the Intervention Mapping protocol, the Theoretical Domains Framework (TDF), and the Capability, Opportunity, Motivation, and Behaviour (COM-B). They help with educational materials and questionnaires for asthma control (Blakey et al. 2018).

Mobile apps or web-based apps are software programs that interact with patients with a visual user interface. They can be used for reminding, feedback on adherence, answering questions, etc. (Milne-Ives et al. 2021; Mosnaim et al. 2021). An example is the Juli app developed by a multidisciplinary team, which includes a game with questionnaires about shortness of breath and advice (Kandola et al. 2024). Other asthma-related mobile apps include AsthmaMD, Kiss myAsthma, ASTHMAXcel, and eAMS. (Jaimini 2018; Kandola et al. 2024). A more sophisticated kHealth system consists of a mobile app, Fitbit to monitor activity and sleep; Microlife Peak Flow, kHealth cloud for storing personal health data, and kHealth Dashboard to interactively visualise collected data (Jaimini 2018; Venkataramanan et al. 2019). The Fitbit Inspire V.2 smartwatch and apps are able to record heart rate, step counts, variability during sleep, breathing rate, skin temperature, oxygen saturation, and predict asthma worsening (Chan et al. 2024). The MASK-air app (www.mask-air.com) is freely available in 27 countries, which comprise a daily monitoring questionnaire assessing daily asthma and daily medication use. Information on the app is used to compute two symptom-medication scores: the combined symptom-medication score (CSMS) and the electronic daily control score for asthma (e-DASTHMA) (Sousa-Pinto et al. 2023). App-based interventions became very common, especially for younger asthmatics (Milne-Ives et al. 2021). Adolescents can be connected with their pharmacists (ADAPT app) to monitor symptoms and adherence or chat with other asthma patients and their pharmacist. They can watch short educational materials or set medication alarms. CHANGE Asthma app and AsthmaWin app were developed for children to present short videos and games, ensuring proper information and knowledge about the asthma therapy plan and control of symptoms, as well as monitoring symptoms and medication adherence. Internet companies like Apple built software frameworks especially designed to facilitate the creation of healthcare apps (Himes et al. 2016). These are ResearchKit and CareKit. Similarly, Verily is a Google framework focusing on health improvement (https://verily.com/). The disadvantage of apps is in the fact that most of them are in the English language and cannot be used by low-literate patients or patients that do not speak English (Franzmair et al. 2021).

Short messages and other messaging platforms can be used for sending messages to improve adherence through reminders for medicine intake, educational, and behavioural messaging (Ferrante, 2021).

Computer games or programs are orientated towards motivation, interactive inclusion of children, stimulating engagement through education, and reinforcing adherence behaviour (like MyMediHealth) (Milne-Ives 2021; Chan et al. 2022). 'Serious games' (SGs) educate children through different asthma-connected situations and give vital information through interactive environments similar to real-life situations (Abraham et al. 2020; Poot et al. 2023). By playing games, children explore asthma self-management, learn how to manage critical situations, avoid allergens, take medicines, and prevent severe symptoms, exacerbations, and hospitalisations. The persuasive game Ademgenoot is intended to encourage people with asthma to take their medication regularly (Poot et al. 2023). The InspirerMundi app is developed to transform adherence to inhalers into a positive experience through game and social support (Jácome et al. 2021). Ademgenoot achieves this by focusing on the positive effects of taking the daily medication. Moreover, the game offers the patients a six-week challenge, and in this period visualises inhaler use in a playful way to make the effect of the medication visible and to stimulate engagement with the game and thus use of their inhaler (Jácome et al. 2021).

Interactive voice response systems are computer-linked telephone intervention system used for organising schedules, perform, receive, record phone calls, which can be used to promote adherence (Chan et al. 2022).

Telemedicine is a new way of treating distant patients. The availability of online communication platforms contributes to replacing in-person visits with virtual consultations. Such an approach is virtually important for remote areas, patients in severe states, epidemics, and other social barriers (Aggelidis et al. 2024). Telemonitoring is a computer-based

technology that not only mediates the communication but might also include devices for digital examination, like, for example, stethoscopes, cameras, web platforms, electronic medical records, portable digital spirometers, or peak flow meters (Persaud et al. 2021). Artificial intelligence (AI) algorithms can recognise, amplify, visualise, and record breath sounds with high sensitivity and thus improve diagnosis. The LungHealth Asthma computer-guided consultation (CGC) can be used to review patients remotely and enables an intelligent structured electronic asthma review (Chakrabarti et al. 2023). For the purposes of telemedicine, platforms were created that are integrated into the telemedicine environment with an electronic health record or stand-alone video services (Persaud et al. 2021; Rhee et al. 2014). Examples of integrated platforms are American Well, Intouch Health/Teladoc Solo, and AMD Connect and Care. Examples of standalone platforms include Zoom, Microsoft Teams, Citrix GoToMeeting, Doximity, Polycom RealPresence, Doxy.me, FaceTime, InTouch/Teladoc, American Well, AMD, and Chiron Health.

A summary of digital technologies influence on adherence is presented in Table 2.

Table 2. Groups of digital technologies in asthma adherence.

Group	Examples	Adherence influence
Online platforms	Virtual Asthma Clinic	Exchange of data for adherence to therapy and monitor asthma state.
	MyMediHealth	Connects physicians and patients.
	AsthmaVillage	Helps patients to take appropriate medication and reminds them.
	AsthmaTuner	Support medication management.
	Mobistudy	Assess asthma severity and quality of life.
	Inspire	Help for a personal action plan.
		Predict asthma attacks.
		Enable self-monitoring of asthma symptoms and lung function.
		Provide recommendations based on the characteristics of symptom control.
		Patients can connect and provide support to one another.
		Enable online discussions and education.
		Build patient data registries.
Computer-based platforms	Mapping protocol	Record information and patient data for medicine intake and therapy follow-up.
	Theoretical Domains Framework (TDF)	Provide home monitoring and adherence advice.
	Capability, Opportunity, Motivation, and Behaviour (COM-B)	Ensure educational materials.
		Evaluate quality of life and asthma severity symptoms through questionnaires.
Short messages	SMS	Remind for medicines intake.
		Provide educational instructions.
		influence behaviour through behavioural messaging.
Mobile apps	Juli	Interact with patients with a visual user interface.
	AsthmaMD	Remind and provide feedback on adherence.
	Kiss myAsthma	Answer questions.
	ASTHMAXcel,	Store and visualise clinical data.
	eAMS	Assessing daily asthma symptoms and daily asthma medication use.
	ResearchKit	Compute symptom-medication scores.
	CareKit	Connect with physicians and pharmacists.
	Similarly	Enable chat with other asthma patients and their healthcare providers.
	Verily	Present short videos and games.
		Ensure proper information and knowledge about the asthma therapy plan and control of symptoms.
		Monitor symptoms and medication adherence.
Computer games	'Serious games'	Stimulate engagement through education and reinforcing adherence behaviour.
	Ademgenoot	Educate children through different asthma-connected situations in real life.
	InspirerMundi	Educate on how to manage critical situations.
		Inform about the risks in the environment.
		Encourage people with asthma to take their medication regularly.
		Transform adherence behaviour through game and social support.
		Motivate people with mild asthma to adhere to medications.
		Visualises inhaler use in a playful way.
Interactive voice response systems		Organising clinical visits,
		Receive and record phone calls, which can be used to promote adherence.
Telemedicine	LungHealth Asthma	Replacing in-person visits with virtual consultations.
	American Well	Might enable digital examination. Artificial intelligence (AI) algorithms can recognise, amplify, visualise, and record breath sounds with high sensitivity and thus improve diagnosis and influence adherence.
	Intouch Health/Teladoc Solo	Review patients records remotely and enable an intelligent, structured electronic asthma review.

Discussion

In this study we aimed to analyse the technological and digital innovations in asthma care aimed at improving patients' adherence. Advances in digital technology are offering new avenues. Technological improvements are orientated towards inhalers and inhalation techniques. The digital component in the technological innovations is added with the purpose of memorising for patients for inhalation or counting the inhalations to connect with physicians and report clinical results.

Fully digital innovations provide more opportunities to improve patients' adherence through the possibility to directly influence therapy, record results, build databases with treatment outcomes, engage psychologically and emotionally, consult virtually, etc. In line with the recommendations from other studies, virtual technologies have the capabilities to provide structured, systematic, and contemporary education to patients, which is a basis of adherence improvement (Fink 2005).

We realise that the separation of new digital technologies into two groups might be artificial, but many of the articles included in this review focused either on inhalers with digital components or on fully digital technologies (Levy et al. 2024; Bosnic-Anticevich et al. 2023; Jansen et al. 2021; Faber et al. 2023; Jácome et al. 2021). The plethora of articles have been devoted to particular new interventions with the aim of comparing them with the already existing technologies and proving their effectiveness (Hui et al. 2022; Blakey et al. 2018; Ainsworth et al. 2019; Murphy et al. 2021; Jaimini et al. 2018; Chan et al. 2024; Persaud et al. 2021).

There is no doubt that new technologies will continue to be developed in the future in the field of improving adherence to therapy in asthmatics. The challenge in front of them will be to better monitor adherence and to build predictive capabilities to translate intermediate results into a long-term system improvement (Salles et al. 2024; Rajaguru et al. 2023; Hein et al. 2020).

Proper inhalation and counting of doses are a permanent challenge, especially for children and adolescents. Therefore, we can assume that inhalers will be further modernised with devices that review successful dosing and memorise medicine intake, store data for proper use, and advise on non-adherence. Healthcare professionals might feel overloaded with the necessity to analyse huge amounts of clinical data, communicate virtually in addition to the usual clinical examination, and might need further support from different healthcare professionals, like pharmacists in case of non-adherence, or nurses (Torous et al. 2022).

For asthma patients, digitally collected real-time data on adherence and related symptoms are important, despite the overburden for physicians (Mokoka et al. 2017). Real-time data can be used by healthcare professionals to distinguish between changes in lung function due to poor adherence and indicators of disease progression. Storage of clinical data on platforms allows an exchange of experience between physicians, building health literacy and responsible behaviour from patients' side (Chan et al. 2015; Moloney et al. 2023).

Advancement of technologies is associated with overcoming several challenges. Processing data from different sources needs complex technical solutions (Marwaha et al. 2022). Building and maintaining digital technologies is a costly process. Many of the newly created digital technologies are not validated and even tested before introduction (Gomis-Pastor et al. 2024). They are developing with time, but their medical suitability should be revised by experienced teams. Real-world databases might change the routine clinical practice (Blonde et al. 2018).

This study was introductory and covered long-term periods with a significant number of technological improvements. We do not go into detailed descriptions of each technology because many of them were described in the reviewed articles. Our primary goal was to highlight major tendencies and gather available information about the current state and future directions in technology improvement in the area of asthmatic adherence to therapy. The limitation of this study is the search in PubMed only. Partly to overcome this limitation, we include articles from the reference list of the selected study, as well as recommended related studies from the database.

Conclusion

Technological improvements in asthma medication adherence are focused on inhalers and inhaler techniques. Digital solutions are orientated toward improvement of inhalation technique, counting inhalations, exchange of information with physicians, and reporting clinical outcomes.

Fully digital innovations like electronic platforms, apps, telemonitoring, games, etc. provide more opportunities to improve patient adherence, mostly orientated towards direct influence on therapy, recording of results, building databases of treatment outcomes, psychological and emotional engagement, virtual counselling, and provision of structured, systematic, and up-to-date patient education, which is the basis for improving adherence.

Additional information

Conflict of interest

The authors have declared that no competing interests exist.

Ethical statements

The authors declared that no clinical trials were used in the present study.

The authors declared that no experiments on humans or human tissues were performed for the present study.

The authors declared that no informed consent was obtained from the humans, donors or donors' representatives participating in the study.

The authors declared that no experiments on animals were performed for the present study.

The authors declared that no commercially available immortalised human and animal cell lines were used in the present study.

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Author contributions

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Data availability

All of the data that support the findings of this study are available in the main text or Supplementary Information.

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Supplementary material 1

Selected articles

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