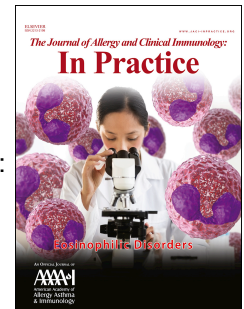


Journal Pre-proof

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A Systematic Review

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PII: S2213-2198(21)00155-0

DOI: <https://doi.org/10.1016/j.jaip.2021.01.027>

Reference: JAIP 3404

To appear in: *The Journal of Allergy and Clinical Immunology: In Practice*

Received Date: 16 November 2020

Revised Date: 13 January 2021

Accepted Date: 14 January 2021

Please cite this article as: Doshi H, Hsia B, Mowrey W, Jariwala SP, Impact of Technology Based Interventions on Patient Reported Outcomes in Asthma: A Systematic Review, *The Journal of Allergy and Clinical Immunology: In Practice* (2021), doi: <https://doi.org/10.1016/j.jaip.2021.01.027>.

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**Impact of Technology Based Interventions on Patient Reported Outcomes in Asthma: A
Systematic Review**

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Conflicts of Interest: None

Funding: This work was supported by the AHRQ award. Grant Number R18 HS025645.

Word Count (Text): 2296

Word Count (Abstract): 242

Figures: 1

Tables: 3

Key Words: Asthma; Technology; Patient Education; Asthma Healthcare Utilization; Asthma
Knowledge; Asthma Quality of Life; Underserved Populations

Abbreviations:

PRO (patient reported outcome)

TBI (technology based intervention)

NAEPP (National Asthma Education and Prevention Program)

46 PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis)

47 ED (Emergency department)

48 ACQ (Asthma Control Questionnaire)

49 ACT (Asthma Control Test)

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Abstract

Background: Technology based interventions (TBIs) can improve asthma management by facilitating patient education, symptom monitoring, environmental trigger control, comorbid condition management, and medication adherence. Collecting patient reported outcomes (PROs) can identify effective interventions and ensure patient-centered care, but it is unclear which TBIs have been formally evaluated using PROs.

Objectives: We aim to: 1) identify the TBIs that have been evaluated in clinical trials using PROs; 2) identify the most commonly used PROs in these trials; and 3) determine the impact of TBIs on PROs in the management of chronic asthma.

Methods: We searched PubMed and Clinicaltrials.gov databases for studies published in English between January 2000 and February 2020 using the following search criteria: “asthma,” “IT-based interventions,” “information technology,” “technology,” “dyspnea,” “patient reported outcomes,” “PROs,” “telehealth,” “telemedicine,” and “mobile devices”. Two independent reviewers screened the studies and determined study inclusion. Studies were examined for the types of interventions used, the types of PROs collected, and outcomes.

Results: The final analysis included 14 clinical trials with either 1, 2, or 3 arms. Five different types of TBIs were identified, most commonly involving multimedia education. Four different categories of PROs were identified, most commonly involving treatment self-efficacy. Positive

outcomes in at least one PRO domain were reported in 12/14 studies. Pooled meta-analysis was not possible due to the heterogeneity of PRO instruments across studies.

Conclusion: TBIs improve patient reported outcomes overall in asthma patients. Future trials investigating TBIs should include standardized PROs as endpoints to better clarify this relationship.

Highlights

1. What is already known about this topic?

- a. Many technology-based interventions (TBIs) have been used for asthma management, but their impact on patient reported outcomes (PROs) is unclear.

2. What does this article add to our knowledge?

- a. TBIs improve patient reported outcomes (PROs) overall, but comparing interventions across studies will require widespread standardization of PROs in clinical trials.

3. How does this study impact current management guidelines?

- a. Management guidelines should include TBIs to improve certain aspects of asthma management, especially treatment self-efficacy. Guidelines should also encourage the use of standardized PROs in clinical trials.

Introduction

Asthma is a chronic respiratory condition characterized by reversible airflow obstruction, airway inflammation, and hyperresponsiveness.¹ Over 300 million people suffer from asthma across the globe and 25.7 million of those patients reside in the United States.² Effective management of this disease requires the identification of potential factors that may impact a patient's disease burden. The National Asthma Education and Prevention Program (NAEPP) Expert Panel describes four principal components of asthma management: assessing and monitoring asthma severity and control; education for a partnership in care; control of environmental factors and comorbid conditions; and medications.³ Tools that help achieve these four goals can reduce the impairment of pulmonary function, decrease the risk of future asthma exacerbations, and improve quality of life.

Technology based interventions (TBIs) can help achieve the goals outlined by the NAEPP. Online portals, for example, can streamline the process of monitoring symptoms and assessing asthma management goals. Multimedia (videos, graphics, interactive animations) can make asthma education more effective and accessible for patients with limited time or resources.⁴ Telehealth can improve not only asthma management, but also management of comorbid conditions that may impact asthma control.⁵ Adherence monitoring devices can help increase the effectiveness of pharmacologic therapies.^{6,7} As technology continues to develop, a growing number of interventions will become available for clinicians to use. To focus efforts optimally, clinicians should use interventions that have been validated in clinical trials and shown to improve outcomes. Changes in laboratory values, imaging, or pulmonary function tests,

however, may not always reflect subtle changes in a patient's condition. Instead, a more patient centered approach including patient reported outcomes (PROs) might help clinicians deliver high quality care and promote shared decision-making.

PROs facilitate the assessment of disease burden and are reported directly by the patient. Several types of PROs exist, including quality of life, disease control, and attitudes about medications.⁸ Increasingly, clinicians are starting to recognize the value of PROs in asthma management and regulatory agencies commonly include PROs in the process of approving drugs and devices.⁹ For this reason, randomized controlled trials are also starting to include PROs as endpoints. The objectives of this systematic review are as follows: identify the TBIs that have been evaluated in asthma clinical trials using PROs as endpoints; identify the PROs most commonly used in these trials; and determine the impact of TBIs on PROs when compared to usual care in patients with asthma. To date, a study assessing these aims has not been performed, though similar studies have been performed for diabetes.¹⁰ This systematic review aims to encourage the adoption of technologies that improve PROs and guide the development of further technologies for improved medication adherence and more patient centered healthcare delivery.

Methods

The reporting of this systematic review was done in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) Guidelines, except for several components. Components of the PRISMA guidelines referring to meta-analysis or pooled analysis were not applicable to our review and were not followed. A protocol for this review was not registered with a database for systematic reviews.

Eligibility criteria

This review included studies published in English between the years January 2000 and February 2020 that investigate the impact of TBIs on patient reported outcomes in asthma. We included original study articles and did not include review articles. Studies were included if they met the following inclusion criteria: the study utilized a TBI, including computers, mobile phones, tablets, or remote electronic medication monitoring devices; the study collected patient reported outcomes; and the patient reported outcome was a primary or secondary outcome of the study. Clinical studies that met our search criteria were selected for review. Identified studies were uploaded into Endnote and duplicates were removed.

Information Sources and Search Strategy

We searched the PubMed and ClinicalTrials.gov databases using the following keywords: “asthma,” “IT-based interventions,” “information technology,” “technology,” “dyspnea,” “patient reported outcomes,” “PROs,” “telehealth,” “telemedicine,” and/or “mobile devices.” In PubMed, the search was further refined using the “AND” and “OR” functions as follows:

“((asthma) AND (patient reported outcome) AND ((Information technology) OR (IT Intervention) OR (mobile device) OR (technology) OR (telehealth) OR (telemedicine)))”.

Study Selection

Two independent reviewers (HD, BH) selected the studies to include in the analysis based on a multi-step process. First, studies were screened based on title and abstract. If either reviewer thought that a study might meet inclusion criteria based on the title and abstract, the study was advanced to independent full-text reviews by both reviewers. If both reviewers agreed that the study met inclusion criteria after full-text reviews, then the study was included in the final analysis. If the two reviewers disagreed about the inclusion of a study, a deliberation was performed to reach consensus. A third reviewer would only be considered if consensus could not be reached by deliberation.

Data Extraction

Included studies were analyzed independently by two of the authors (HD, BH) regarding the following data items: age group of participants (adult, pediatric, both, or not specified); number of participants included in the study; intervention(s) performed; outcome(s) analyzed; and study results.

For the studies with two or three arms, a positive outcome was defined as a statistically significant improvement in the TBI arm compared to the control arm. Alternatively, if the study analyzed the intervention arm based on non-inferiority and both arms were effective, a positive outcome was defined as a lack of statistical difference between arms. For single arm studies, a

statistically significant improvement from baseline to outcome time point was considered a positive outcome.

Data analysis

The characteristics of the studies including types of intervention and PRO were summarized. The number of studies demonstrating positive outcomes were computed for each PRO. Quantitative meta-analysis of the studies was not possible because the instruments used to collect PROs were highly variable between studies.

Results

Search Results and Dataset Inclusion

The database searches identified 959 unique citations, of which 8 were excluded for unfinished or unavailable results (Figure 1). The remaining 951 studies were screened based on titles and abstracts and 921 were excluded. An additional 16 articles were excluded after full text review. Thus, 14 studies (3062 participants, 8 countries) were included in the analysis.¹¹⁻²⁴

The 14 studies included are summarized in table 1. The median number of participants among the studies was 125, with 10 publications studying pediatric populations and 4 studying adult populations. Of the 14 studies, ten were randomized controlled trials with two arms; two were randomized controlled trials with three arms, and two were single arm studies. Seven studies were conducted in the United States while the other seven were conducted internationally. All studies were conducted in urban environments. For all studies, the intervention arm was a TBI. For studies with two arms, the control arm was “usual care”. This was defined as continuation of usual physician visits without access to the intervention website or other content. For studies where the intervention required in-person use of multimedia or electronic content, the control arm participants engaged in other in-person activities, including playing non-educational games, watching blank videos, browsing generic non-personalized websites, and receiving verbal demonstrations from providers. For studies with three arms, the TBI arm was compared to the arm that did not have access to the TBI when assessing outcomes.

Interventions and Patient Reported Outcomes

Interventions and patient reported outcomes used in each study are summarized in Table 2. Five different types of TBIs were identified among the studies: internet based self-reporting tools, electronic medication monitoring devices, electronic diaries, multimedia education, and telehealth visits. The intervention used by ten studies could be classified under one of the above five categories, whereas four studies used multi-component interventions involving multiple categories. None of the interventions was via a smartphone app. The most common intervention was multimedia education, used in 9 of the studies as either part or all of their intervention. The least common intervention was a medication monitoring device, used in only one study.

Similarly, four different types of patient reported outcomes were collected among the studies: asthma severity, asthma control, treatment self-efficacy, and quality of life. All studies collected multiple patient reported outcomes. Treatment self-efficacy was the most commonly assessed domain and asthma severity was the least commonly assessed domain, used in 11 and 1 of the studies, respectively. Self-efficacy was defined based on the available literature as a person's confidence in their ability to perform the appropriate action in a given situation.²⁵⁻²⁷

Impact of Interventions on Patient Reported Outcomes

The outcomes of each study and each outcome domain are summarized in table 3. Of the 14 studies, 12 showed a positive outcome in at least one of the patient reported outcome domains. The outcome domain that most consistently improved with a TBI was treatment self-efficacy, with improvement seen in 73% of studies using the domain. The outcome domain that showed

the least improvement was asthma severity, which did not improve in any of the studies where that metric was collected. The instruments used to measure PROs varied widely between studies (see discussion). In addition to collecting PROs, many studies also collected clinical outcomes including hospitalizations and ED visits. For reference, this data is also provided in table 3.

Discussion

This systematic review of 14 studies supports the use of TBIs to enhance asthma management and improve patient reported outcomes (PROs). Most interventions included in this study used some form of multimedia education, including educational videos, interactive animations, pictures, computer games, or other web-based content. This is consistent with the published literature, where the majority of TBIs that have been described for asthma involve giving the patient some form of self-management information.²⁸ Other interventions, particularly smartphone apps or electronic diaries, were not well represented in this study. In the available literature, many smartphone apps and electronic diaries have been described, including over 200 mobile applications on Android or Apple, but very few been validated through clinical trials. Of the few validated mobile applications, most are not publically available and have not been validated in multiple settings.²⁹ Ultimately, relative to the number of TBIs that have been described for asthma management, our study includes only a small portion. The lack of these other interventions in our study reflects a need for more clinical trials evaluating these TBIs with a focus on patient reported outcomes. As the options for TBIs continue to increase, the inclusion of PROs in clinical trials will be critical in ensuring patient centered care.

The assessment of each PRO was highly variable across studies. For example, asthma control was occasionally assessed through known questionnaires like the Asthma Control Questionnaire, Asthma Control Test, and Children's Health Survey for Asthma, but was more often assessed through miscellaneous survey questions assessing daytime symptoms, nighttime symptoms, missed school days, frequency of flares, and symptom free days. Asthma severity was only seen once among our studies, and was assessed using a miscellaneous 3-point scale survey. Self-

efficacy was our most commonly assessed PRO domain, usually through miscellaneous survey questions about medication adherence, asthma knowledge, rescue inhaler availability, peak flow meter usage, or confidence in responding to an asthma emergency. In our study, quality of life was assessed through some well-known surveys including the Asthma Quality of Life Questionnaire but was also more often assessed through miscellaneous survey questions.

This pattern of collecting PROs through a large variety of instruments is consistent with the literature. While hundreds of generic PROs have been described, only a small portion have been well validated.³⁰ The Asthma Quality of Life Questionnaire, for example, is among the oldest PROs used in asthma, and also one of the best validated.³¹ Other well-known and validated PROs include the Asthma Control Test and Asthma Control Questionnaire, but most metrics used in our studies were non-validated miscellaneous survey questions as described above.^{30, 32, 33} Even when studies appeared to use surveys with the same name, further investigation revealed that the actual surveys were quite different. Studies 3 and 7, for example, both used an “Asthma Control Questionnaire”, but the scales and questions used in the studies differed. One study defined a positive outcome as a high score in their ACQ while the other study used an ACQ that favored a lower score.^{13, 17} Because of this high variability, pooled meta-analysis of the impact of TBIs on PROs was not possible. The use of unvalidated PROs is suboptimal, and some validated surveys are not freely available. A consensus on standardized, freely available PROs for use in clinical trials is essential to better compare the impact of interventions across studies.

Since performing a quantitative and pooled meta-analysis was not possible, we performed a descriptive analysis to show that TBIs can improve patient reported outcomes. Not all outcome

types, however, were equally impacted by TBIs. Of the categories assessed in at least 5 studies, self-efficacy was the most likely outcome domain to improve (improved in 73% of studies). This tendency for improvement in self-efficacy outcomes reflects the types of interventions that were included in this study. As previously mentioned, most interventions in our studies used multimedia education to promote knowledge or compliance, two key barriers to asthma self-efficacy.^{34, 35} Interestingly, as shown in table 3, the clinical outcomes of hospitalizations and ED visits were less likely to improve as a result of the TBIs, despite frequent improvements in patient reported outcomes. This suggests that TBIs may improve the patient's perception of disease burden and the patient's understanding of the disease, but may not actually alter the natural course of the disease. The literature on this is quite conflicted, with some TBIs improving clinical outcomes and others showing no change.²⁸ Further trials will be needed with standardized outcome metrics to better clarify the relationship between TBIs, patient reported outcomes, and clinical outcomes.

This was a systematic review conducted as per the PRISMA guidelines with certain exceptions as stated in the methods.³⁶ The first notable limitation is that the number of included studies is relatively low, underlining the need for future trials to include standardized PROs as endpoints. Furthermore, all studies included in this review occurred in urban areas, so further research will be needed to assess the impact of TBIs on PROs in rural settings. The nature of the technology based interventions used in these studies also prevented blinding, a known limitation of studying some behavioral interventions.³⁷ Prior studies have underscored the importance of blinding in trials with subjective outcomes, like patient reported outcomes, so the lack of blinding in these studies may have been an important source of bias.^{38, 39} For instance, intervention arm

participants may have reported improved outcomes due to social desirability bias or a perception of improved outcomes after exposure to multimedia education, personalized asthma websites, or other interventions.⁴⁰ For these reasons, further correlation in trials that use both PROs and objective clinical endpoints is essential. Despite these limitations, our findings still suggest that TBIs improve PROs. The widespread adoption of standardized PROs will better clarify this relationship by facilitating more robust pooled analysis and the comparison of interventions across studies. Identifying the most effective TBIs will ultimately allow clinicians to better engage patients in their own care and provide more patient centered management of chronic asthma.

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523 **Tables and Figure Legends**

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525 Figure 1: Inclusion and exclusion of studies from targeted literature review

526 Table 1: Summary of included studies

527 Table 2: TBIs and PROs used in each study

528 Table 3: Positive outcomes reported in intervention arm

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Table 1

Study Number	First Author	Year Published	Randomized	Number of Arms	Number of Participants	Age Group	Country	Setting
1	Homer ¹¹	2000	yes	2	137	pediatric	USA	Urban
2	Joseph ¹²	2006	yes	2	314	pediatric	USA	Urban
3	van der Meer ¹³	2009	yes	2	200	adult	Netherlands	Urban
4	Otsuki ¹⁴	2009	yes	3	250	pediatric	USA	Urban
5	Halterman ¹⁵	2012	no	1	28	pediatric	USA	Urban
6	Botngard ¹⁶	2013	yes	2	108	pediatric	Norway	Urban
7	Lim ¹⁷	2014	yes	2	60	adult	Australia	Urban
8	Barthel ¹⁸	2015	yes	1	312	pediatric	Germany	Urban
9	Fiks ¹⁹	2015	yes	2	60	pediatric	USA	Urban
10	Wiecha ²⁰	2015	yes	2	58	pediatric	USA	Urban
11	Arikan-Ayyildiz ²¹	2016	yes	2	78	pediatric	Turkey	Urban
12	Pool ²²	2017	yes	2	608	adult	USA	Urban
13	Bruton ²³	2018	yes	3	655	adult	United Kingdom	Urban
14	Fremont ²⁴	2018	yes	2	113	pediatric	France	Urban

Table 2

Study Number	First Author	Internet Based Self Report	Smartphone App	Adherence Monitoring Device	Electronic Diary	Multimedia Education	Telehealth	Dyspnea Severity	Asthma Control	Self-Efficacy	Quality of Life
1	Homer ¹¹	no	no	no	no	yes	no	yes	no	yes	yes
2	Joseph ¹²	no	no	no	no	yes	no	no	no	yes	yes
3	van der Meer ¹³	yes	no	no	yes	yes	yes	no	yes	yes	yes
4	Otsuki ¹⁴	no	no	yes	no	no	no	no	yes	yes	no
5	Halterman ¹⁵	no	no	no	no	no	yes	no	yes	yes	yes
6	Botngard ¹⁶	no	no	no	no	yes	no	no	no	yes	no
7	Lim ¹⁷	no	no	no	no	no	yes	no	yes	no	no
8	Barthel ¹⁸	yes	no	no	no	no	no	no	no	yes	no
9	Fiks ¹⁹	yes	no	no	yes	yes	no	no	yes	yes	yes
10	Wiecha ²⁰	yes	no	no	yes	yes	no	no	yes	yes	no
11	Arikan-Ayyildiz ²¹	no	no	no	no	yes	no	no	yes	no	no
12	Pool ²²	yes	no	no	no	no	no	no	yes	yes	yes
13	Bruton ²³	no	no	no	no	yes	no	no	yes	no	yes
14	Fremont ²⁴	no	no	no	no	yes	no	no	no	yes	no
Total		5	0	1	3	9	3	1	9	11	7

Table 3

Study	First Author	Dyspnea Severity	Asthma Control	Self-Efficacy	Quality of Life
1	Homer ¹¹	No	Not Assessed	Yes	No
2	Joseph ¹²	Not Assessed	Not Assessed	Yes	Yes
3	van der Meer ¹³	Not Assessed	Yes	No	Yes
4	Otsuki ¹⁴	Not Assessed	No	Yes	Not Assessed
5	Halterman ¹⁵	Not Assessed	Yes	Yes	Yes
6	Botngard ¹⁶	Not Assessed	Not Assessed	No	Not Assessed
7	Lim ¹⁷	Not Assessed	Yes	Not Assessed	Not Assessed
8	Barthel ¹⁸	Not Assessed	Not Assessed	Yes	Not Assessed
9	Fiks ¹⁹	Not Assessed	Yes	Yes	No
10	Wiecha ²⁰	Not Assessed	No	Yes	Not Assessed
11	Arikan-Ayyildiz ²¹	Not Assessed	No	Not Assessed	Not Assessed
12	Pool ²²	Not Assessed	Yes	No	Yes
13	Bruton ²³	Not Assessed	Yes	Not Assessed	Yes
14	Fremont ²⁴	Not Assessed	Not Assessed	Yes	Not Assessed
Total Assessed		1	9	11	7
Total Positive		0	6	8	5

Journal Pre-proof

Figure 1