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MOBILE & WIRELESS HEALTH

Use of Mobile Applications to Increase Therapeutic Adherence in Adults: A Systematic Review

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Abstract

Failure to comply with therapeutic treatments implies negative repercussions for the patient's quality of life, their social environment, and health system. The use of information and communication technologies, especially mobile applications, has favored the increase in global therapeutic adherence figures. The objective of this study is to characterize the use of mobile applications as a strategy to increase therapeutic adherence in adults. A systematic literature review in Web of Science and Scopus was performed following the Preferred Information elements for Systematic Reviews and Meta-analysis. Information such as: the year of publication, the study population, the medical conditions of the participants, the main characteristics or functionalities of the mobile applications, and the methods or tools used to measure treatment adherence were extracted from each included article. The risk of bias was assessed. Twelve randomized controlled trials (RCTs), published in English from 1996 to May 2021, were included. Chronic diseases have been mostly addressed through interventions with mobile applications. The most reported functions of mobile applications were reminders, educational modules, two-way communication, and games. Tools such as: "Morisky Medication Adherence Scale of eight items"; "Medication adherence questionnaire"; "Self-reported adherence"; among others, were used to evaluate and report the treatment adherence. In conclusion, including treatment interventions using mobile applications in clinical practice has proven to be beneficial to improve therapeutic adherence. However, it is necessary to develop high-quality clinical trials (size and duration) to generalize results and justify their use in conventional health services.

Keywords Treatment adherence and compliance · Information technology · Mobile applications · Adult · Systematic review

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Introduction

The World Health Organization (WHO) defines therapeutic adherence as the rate at which an individual's behavior in relation to medicine use, consuming a healthy diet and changing their lifestyle corresponds to the instructions agreed by a health professional and a patient [1]. Adherence differs from *compliance* in the active role played by the patient and the professionals throughout the entire process [2]. Nonadherence to treatment has become an issue in clinical care, which transcends disease; a study estimates that 20–50% of patients do not follow the treatment plan appropriately [3]; a meta-analysis reported the rate of therapeutic nonadherence, on average, was 24.8%, yet it depended on the seriousness of the pathology [4]. The WHO estimates that in developed countries therapeutic adherence to long-term therapies or therapies for chronic conditions, on average, is 50% [1]. Furthermore, it has been discovered that nonadherence concerns not only patients but also the healthcare system in terms of high costs, clinical complications, hospital readmissions and loss of human talent [5]. Poor adherence is responsible for 5 and 10% of hospital admissions, 2.5 million medical emergencies and 125,000 deaths in the United States every year [6].

At present, digital health and the information and communication technologies (ITCs) for health care are used to promote equal and universal access to health services [7]. The WHO acknowledges in its recently published *Global strategy on digital health 2020–2025*, that ICTs are innovation elements and facilitators for ensuring health intervention all over the world [8]. ICTs, in particular mobile health (mHealth), are widely used for remote care, treatment of chronic conditions, communication between health professionals and patients and monitoring of intervention plans [9–12]. Considering this, some systematic reviews discovered that the use of applications for smartphones (APPs) has the advantages of accessibility, lower costs and a variety of functions to treat conditions in the short-term and the long-term. Additionally, other mHealth interventions such as the short message service (SMS) and electronic pill boxes can also have a positive effect on pharmacological adherence [13, 14]. However, there is scant evidence of the use of APPs effectively improving therapeutic adherence under different health conditions.

The main purpose of this systematic review is to describe the APP functions that proved a positive effect on therapeutic adherence, as well as to describe the tools used for assessing adherence and the results thereof. Secondarily, it is to figure out chronicity of APP interventions and to sort them into pharmacological and non-pharmacological interventions.

Methods

Literature review

A systematic literature review was conducted from various databases following the items in the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) [15]. The electronic databases included were the following: Web of Science and Scopus, for studies published between 1996 and May 2021. Moreover, a manual search was carried out among the lists of references of the articles included. The search strategy included combinations of terms related to the use of technologies in health -Telemedicine OR Telehealth OR eHealth OR mHealth-, mobile devices -Mobile Applications OR Smartphone-, adherence to treatment -Adherence OR "Treatment Adherence and Compliance"- and adult population -Adult OR Aged OR Elder. MeSH terms, key words and thesaurus were used for reducing the possibility to miss any relevant studies. The search was restricted to publications in English and Spanish.

Study selection

Following the first search, the selection of studies was made in three phases. First, duplicates of publications were removed by Zotero® software Version 5.0.89 (Center for History and New Media at George Mason University). Second, the titles and summaries were examined according to the following inclusion criteria: studies reporting on relations between the factors of interest –adherence to treatment and mobile applications-, publications written in English and Spanish, articles published in magazines cataloged and reviewed in pairs. Third, the full texts of potentially relevant studies were thoroughly reviewed considering the inclusion and exclusion criteria for final analysis.

Inclusion and exclusion criteria

The inclusion criteria in the review were: adult participants ($\geq$ 18 years), a treatment developed with mobile applications, control groups had to undergo conventional treatment -not using any APP. The experimental and control groups were both provided with data on adherence to treatment, the study design was randomized controlled trial (RCT), the articles were published in English or Spanish and, finally, the results were classified into: types of treatments, major features of the mobile application or tools used for measuring adherence to treatment.

Studies were excluded for they included participants aged under 18, conventional treatments developed for health professionals or results limited to cost utility and cost effectiveness. Also, because they reported adherence to interventions

in health promotion and prevention not considered as treatment plans. Articles issued as summaries, posters and billboard posters for lectures were dismissed as well.

Data collection

Data were collected by means of a customized matrix which included the features of the studies –year and country of the study, study design, sample size, health condition of the population, participants' features, name of the mobile application, APP features; scales or tools used for measuring adherence to treatment.

Risk of bias assessment

The risk of bias helped to assess validity of the results of the study and analyze whether they show reliable evidence for interpretation [16]. Two proofreaders assessed each article here individually. Any disagreement was resolved through discussion between the authors until they reached an agreement. It is considered that the studies' risk of bias is not noticeably clear for an item, as far as the main article did not provide with enough information for proofreaders to be categorical about a high or low risk of bias.

Results

The first search returned 3,025 potentially eligible studies. After removing duplicate, 1,202 studies were examined by their titles and summaries. 63 were considered eligible and their whole contents were read for evaluation purposes. Out of these, 12 studies reported eligible data for inclusion of the analysis [17–28]. The selection process and the reasons for exclusion are stated in flow diagram (Fig. 1).

Study features

Most of the studies were conducted in the last four years (2018–2021) over diverse areas: Asia (41.66%), Europe (33.3%) and North America (25%). RCT sample size varied from 36 to 480, with a median of 117.5. The main health conditions of the patients who received APP-based treatment were: coronary heart disease (25%), cancer (17%), hypertension (17%) and diabetes (17%), among others. Monitoring intervals of APP interventions varied from 12 months (17%) to 0.75 months –3 weeks- (8%) (Table 1).

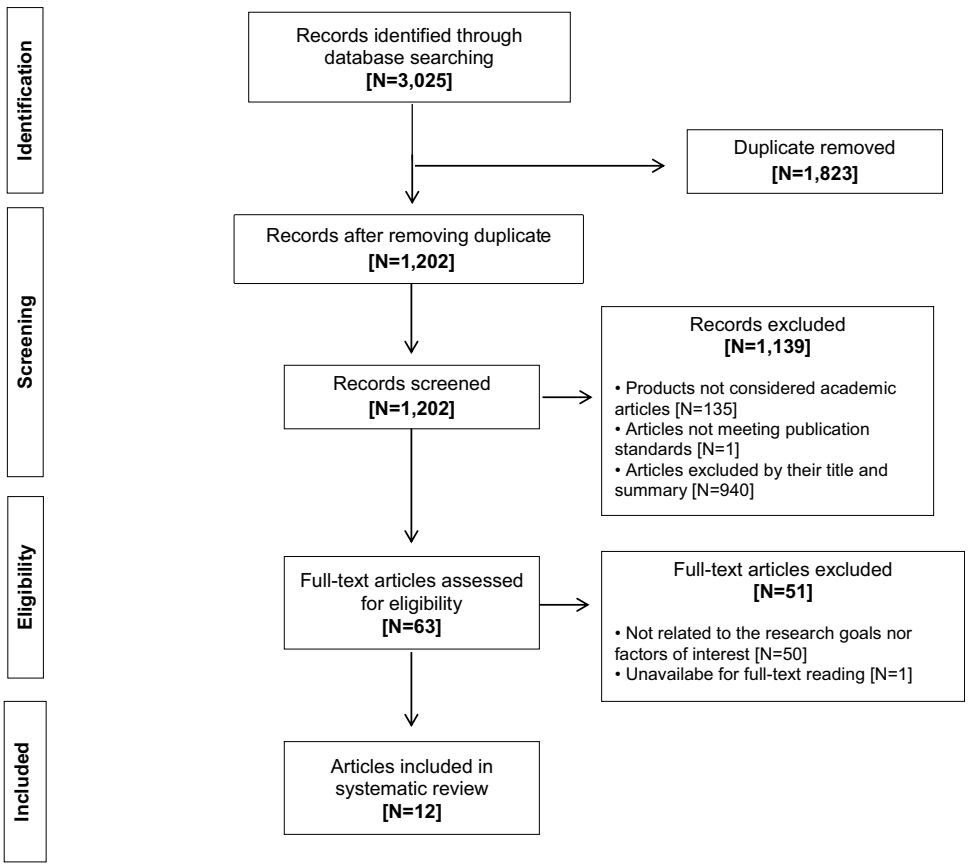

Fig. 1 PRISMA flow diagram for systematic reviews

Table 1 Characteristics of the studies included

Authors	Year of publication	Country where the study was conducted	Target population health condition	Characteristics of the participants at the time of recruitment				Name of the application	Characteristics/Functions of the mobile application	Tools for measuring adherence	Monitoring intervals
				Intervention group		Control group					
				Average age (SD)	N	Average age (SD)	N				
Puig et al. [17]	2021	Spain	HIV	65 ± 3	50	66 ± 3	50	Approp	• **Reports**: progress tracking regarding clinical parameters, including patient history, vaccines, anti-retroviral therapies, medication, pharmacological interactions and graphs on laboratory parameter variations • **Education:** counselling programs about health and diet to prevent hypertension, osteoporosis and diabetes. Motivational tools for promoting specific exercises, smoking cessation • **Reminders:** upcoming appointments with health professionals (HIV and other sections); anti-retroviral medication and associated medication reminder; visual alerts with medication resupply notifications • **Communication:** medical assistance through emails, text messages and video calls	Self-reported adherence (SERAD)	12 months
Karaaslan-Eşer and Ayaz-Alkaya [18]	2021	USA	Cancer	60.33 ± 9.31	42	62.14 ± 9.97	42	OKTED	• **First module:** specific information about handling oral anticancer agents (OAA). Calendar for recording treatment start and end dates. Medication reminder • **Second module**: information about symptoms and symptom management recommendations • **Third module**: frequently asked questions and answers section	Oral Chemotherapy Adherence Scale (OCAS)	6 months
Riegel et al. [19]	2020	USA	Acute myocardial infarction or unstable angina	59.5 ± 11.3	62	57.3 ± 10	68	Wellth	• **Daily emails:** scheduled medication reminders • **Evidence upload**: participants uploaded a picture of the medicine in their hand using the app Wellth every 12 h	Medication intake days / Total amount of days in the period	1 month
Gong et al. [20]	2020	China	Primary hypertension	58.20 ± 7.47	225	59.27 ± 7.43	218	Yan Fu	• **Reminder**: dose and timing of medication and blood pressure measurement • **Information:** suggestions about hypertension	Morisky scale modified 8 (MMS-8)	6 months
Hauser-Ulrich et al. [21]	2020	Switzerland	Continuous or cyclical pain	42.97 ± 12.17	59	44.88 ± 13.50	43	SELMA	**Text-based health chatbot (TBHC)** • **Educational module**: psycho-education from day 1 to day 21 through 7 sequences of text messages a day. Customized messages according to pain intensity and duration • **Intervention module:** from day 22 to end, SELMA offers intervention modules based on participant preferences in the following categories: dysfunctional cognition and behavior; confrontation strategies	Proportion of participants' replies to the total amount of conversations initiated by SELMA	2 months

Table 1 (continued)

Authors	Year of publication	Country where the study was conducted	Target population health condition	Characteristics of the participants at the time of recruitment				Name of the application	Characteristics/Functions of the mobile application	Tools for measuring adherence	Monitoring intervals
				Intervention group		Control group					
				Average age (SD)	N	Average age (SD)	N				
Boyd et al. [22]	2020	USA	Coronary heart disease	60.0 ± 7.1	21	60.9 ± 6.9	24	MyIDEA	• **Educational module**: customized with narrations by patients to encourage compliance with medication as part of a Dual Antiplatelet Therapy (DAPT) • **FAQs module:** immediate answer to common questions following proceedings	Morisky scale modified 8 (MMS-8)	3 months
Zhu et al. [23]	2020	China	Schizophrenia	31.71 ± 7.23	42	31.33 ± 6.95	42	WeChat	• **Reminders**: medication reminder 2–4 times a day • **Education:** about managing disease (medication, symptoms, cognitive rehabilitation and psychosocial strategies), once a week	Medication Adherence Questionnaire (MAQ)	6 months
Höchsmann et al. [24]	2019	Switzerland	Type 2 Diabetes	56 ± 5	18	58 ± 6	18	Mission: Schweinehund	• **Games:** trainings and physical activity promotion (recommendations). Trainings included in the game consist of 130 exercises involving strength, endurance, balance and flexibility, and consider daily physical activity as well. The game keeps track and monitors activity through sensors in the mobile phone (camera, accelerometer and gyroscope)	Usage data	6 months
Huang et al. [25]	2019	Singapore	Type 2 Diabetes	51.5 ± 22–69	50	52 ± 28–67	51	Medisafe	• **Reminders:** schedule, medication reminder and tracker • **Data exchange and assessment of adherence to medication**	Adherence Starts with Knowledge-12 (ASK-12)	3 months
Kim et al. [26]	2018	Korea	Cancer	49.8	36	52.1	40	ILOVEBREAST	• **Educational module**: education and support to prevent side effects of cancer treatment • **Psychosocial module:** boosting mood and physical activity • **Self-assessment**	Medication Adherence Rating Scale (K-MARS)-Korean version	0.75 months (3 weeks)
Ni et al. [27]	2018	China	Coronary heart disease	No especificado Mayores de 18 años	18	No especificado Mayores de 18 años	18	WeChat y BB Reminder	• **Group chat:** through live chats, video calls, text messages, file exchange and voice notes •**Reminders**: through BB Reminder	Voil's Medication Nonadherence Rating Scale	2 months
Márquez Contreras et al. [28]	2018	Spain	Primary hypertension	57.7 ± 9	77	57.08 ± 10	77	AlerHTA	• **Record**: personal data; doctor's advice on the treatment prescribed and posology • **Reminders:** medication reminder • **Calendar:** appointments/events	(Total amount of pills taken / Total amount of pills to be taken) *100	12 months

Table 2 Results obtained using measurement tools for adherence to treatment

Study	Measurement tools for adherence	Outcome description	*p*-value
Puig et al. [17]	Self-reported adherence (SERAD)	Without significant changes in adherence over the last week (week 48)	p = 0.49
Karaaslan-Eşer and Ayaz-Alkaya [18]	Oral Chemotherapy Adherence Scale (OCAS)	OCAS scores of the intervention group increased in each phase (statistically significant variation between the first scores and the records after months 1, 3 and 6)	p = 0.001
Riegel et al. [19]	Medication intake days / Total amount of days in the period	Regression test confirmed reduction in adherence of the control group, median reduction 0.05 per period (p = 0.16, 95% CI: -0.11, 0). Whereas records of the intervention group showed -0.0023 (p = 0.92; 95% CI: -0.08; 0.02) The difference in adherence trends between the groups was not statistically significant (estimation = 0.04; p = 0.18; 95% CI: -0.03; 0.11)	p = 0.18
Gong et al. [20]	Morisky scale modified 8 (MMS-8)	Adherence to medication improved in both groups (control group: p = .048- intervention group: p = .00) The intervention group showed better adherence to medication than the control group after comparing adherence measurement outcomes in the last month (p = 0.004)	p = 0.004
Hauser-Ulrich et al. [21]	Proportion of participants' replies to the total amount of conversations initiated by SELMA	There were no significant variations in adherence rates between the intervention group and the control group (t 37 = 1.81, p = 0.08)	p = 0.08
Boyd et al. [22]	Morisky scale modified 8 (MMS-8)	Without significant variations in the average score on knowledge and medication-adherence-related beliefs in the two visits, following Morisky's questionnaire	p = 0.50
Zhu et al. [23]	Medication Adherence Questionnaire (MAQ)	Significant differences in medication adherence of the two groups (F = 28.087, p < 0.001, ηp2 = 0.255) with marked effect	p = 0.001
Höchsmann et al. [24]	Usage data (Steps, completed and cancelled trainings, usage patterns and time in a day)	The intervention group used games during 131.1 min. a week (SD 48.7) for walking and 15.3 min. a week (SD 24.6) for strength training It shows a positive relation between the amount of training through the game (min) and the change in the total Intrinsic Motivation Inventory score (beta = 0.0028; 95% CI: 0.0007–0.0049; p = 0.01)	p = 0.01
Huang et al. [25]	Adherence starts with knowledge-12 (ASK-12)	ASK-12 scores of the intervention group decreased, and they increased among the control group participants Following the first adjustments "years suffering from diabetes" and "ASK-12 first score", ASK-12 pre-post "change scores" were statistically significant (p = 0.01), the intervention group with score 4.7 points (1.2–8.2) below the control group score	p = 0.01
Kim et al. [26]	Medication adherence rating scale (K-MARS)-Korean version	The intervention group showed better compliance of medication in comparison with the control group (K-MARS 7.6 ± 0.7 against 6.5 ± 0.5; p < 0.001)	p = 0.001
Ni et al. [27]	Voil's Medication Nonadherence Rating Scale	Adherence to medication increased in both groups after 30 days of monitoring, the experimental group record being higher (M = -1.35, SD = 2.18) than the control group record (M = -0.69, SD = 1.58). However, this difference between the two groups was not statistically significant (p = 0.33)	p = 0.33
Márquez Contreras et al. [28]	(Total amount of pills taken / Total amount of pills to be taken) *100	Significant differences between the groups, favorable to the intervention group, regarding Overall adherence (p = 0.01), Adherence to single daily dose (p = 0.001), Adherence to correct intake time (days p = 0.05 and hours p = 0.001) and Adherence to therapy (p = 0.05)	p = 0.001 p = 0.01 p = 0.05

Characteristics of the Mobile Applications

The studies defined the features of the APP used for intervention to increase therapeutic adherence. 67% of the studies (n = 8) reported on the reminder system, which allows to set a calendar [18, 28] and send alarms to patients at scheduled times to remind them to take their medication and of upcoming appointments, among others [17–28]. 58% (n = 7) referred to automated education, which is based on providing the user with information about the condition, symptoms, medicine use, importance of following the treatment, side effects of medication, psycho-social and confrontation strategies [17, 18, 20–23, 26]. Almost 17% (n = 2) of the studies mentioned the frequent asked questions [18, 22]. The function related to uploading evidence was reported by 8% of the studies –this is about sending a picture of the medicine in the patient's hand through the APP [19]. Furthermore, a study combined intervention and bidirectional communication functions, by means of emails, text messages or video calls [17]. To conclude, one study used an APP for intervention through a game. The game included training options, recommendations to promote physical activity, tracking and treatment monitoring [24]. Information about "Patients use of the mobile applications" in Supplementary Table.

Tools for Measuring Adherence to Treatment

Two out of the twelve studies measured adherence according to the Morisky Medication Adherence Scale [20, 22]. The rest of the studies used other tools: Medication adherence questionnaire [23]; Self-reported adherence [17]; Oral Chemotherapy Adherence Scale [18]; Adherence starts with knowledge-12 [25]; Medication adherence rating scale [26]; Voil's Medication Nonadherence Rating Scale [27]. Some of the remaining studies reported on adherence based on the number of medicines taken [19, 28], whereas others took into consideration the APP usage data [21, 24] (Table 2).

Risk of Bias

The quality of twelve RCTs [17–28] was summarized in a table of risk of bias (Table 3). Ten studies [17–24, 26, 27] reported on the generation of random sequences. A study mentioned that participants where blinded [17]. Additionally, four studies remarked that a perfect blinding was not possible [18, 21, 22, 25]. A study did not refer to whether the results were influenced by the blindness [26] and six studies introduced partial data thereof [17–21, 27, 28].

Table 3 Summary of the risk of bias assessment

	Selection bias		Performance bias	Detection bias	Attrition bias	Reporting bias	Other biases
	Sequence generation	*Allocation concealment*	*Blinding of study participants and personnel*	*Blinding of outcome assessors*	*Incomplete outcome data*	*Selective outcome reporting*	*Other biases*
Puig, J., Echeverría, P., et al. [17]	●	●	†	‡	●	●	●
Eşer, A. K., & Alkaya, S [18]	●	‡	†	‡	●	●	●
Riegel, B., Stephens-Shields, A., et al. [19]	●	†	●	●	●	●	●
Gong, K., Yan, Y., et al. [20]	●	†	†	‡	●	●	●
Hauser-Ulrich, S., Künzli, H., et al. [21]	●	‡	†	†	●	●	●
Boyd, A. D., Ndukwe, C. I., et al. [22]	●	‡	●	‡	●	●	●
Zhu, X., Li, M., et al. [23]	●	†	●	●	●	●	●
Höchsmann, C., Infanger, D., et al. [24]	●	†	●	†	●	●	●
Huang, Z., Tan, E., et al. [25]	†	‡	●	●	●	●	●
Kim, H. J., Kim, S. M., et al. [26]	●	†	‡	‡	●	●	●
Ni, Z., Liu, C., et al. [27]	●	†	†	‡	●	●	●
Márquez, C. E., Márquez, R. S., et al. [28]	†	†	†	‡	†	●	●

Low risk of bias	●	Bias unlikely to alter the outcomes significantly
Unclear risk of bias	†	Bias raising doubts about the outcomes
High risk of bias	‡	Bias seriously affecting outcome reliability

Discussion

This review served for identification of a series of APP functions which showed a positive effect on therapeutic adherence. Automated educational functions were the most used in all applications resulting in favorable changes towards therapeutic adherence. This has been supported by several studies proving that those educational interventions help behavioral change by improving communication between patients and health professionals, which increases therapeutic adherence as well [29, 30]. The second APP function in rank was the medication reminder. A number of studies have considered this strategy with the aim of ensuring compliance of pharmacological treatment [31, 32]. However, there are some limitations regarding the use of reminders: people may become dependent on them for taking their medicines, which could lead to failure because of error in the APP, Internet access issues, low battery or inattention. In light of this, APP intervention shall include behavioral strategies to encourage patient autonomy and self-management of treatments, causing the APP to be simply a support tool.

There was also evidence on why an APP designed to improve therapeutic adherence should consider including other functions such as a calendar [to remember start and end dates of treatments, appointments, tests and therapies], bidirectional communication with health professionals and games offering feedback about the knowledge acquired. Finally, it is worth highlighting that a dynamic, interactive and creative presentation of the information guarantees better comprehension among people with low literacy levels and bridges the access gap in basic communication.

As for the tools for measuring adherence to treatment, they were of diverse types and most of them were validated psychometric tools, which enabled the identification of patterns of adherence after detecting the profiles of those patients likely to adhere. Nevertheless, it is important to always remember that the outcomes rely on the patient's subjectivity and honesty. Therefore, they should be matched according to the results from medical tests to say whether the findings are trustworthy. Furthermore, four studies made use of other indirect methods such as the percentage of medicines taken over a period, the total amount of medicines yet to be taken or data usage indicators. The method based on the percentage has been validated and it is considered as an objective and reliable method [33, 34]. Nonetheless, this method does not allow to identify possible reasons for treatment incompliance or withdrawal. Last, choosing the right measurement method in essential to ensure trustworthy results, since the decision shall be made based on the health condition, the type of intervention and the behavior subject to assessment. Besides, the method shall avoid the overestimation and underestimation of the results.

The analysis of the measurement instruments showed that therapeutic adherence improves in direct proportion to factors like intervals between monitoring and the type of intervention. These two factors are matched to statistically significant changes regarding the increase in adherence among the experimental groups. The first one applies to intervals between monitoring: the more patients use the APP, the better adherence to therapy. This is in relation to a study about the consolidation of new habits and the automation of new conducts, which reports that the average time necessary to reach 95% of automaticity is 66 days, ranging from 18 to 254 days [35]. This suggests that APP intervention shall be consistent for people to achieve their automaticity limit with respect to the expected behavior. The second factor concerns pharmacological interventions, as they proved to have greater significance in comparison with the non-pharmacological ones. It is easier to improve medication adherence than achieving a health-related behavioral change. Marilyn Rice acknowledges that providing people with information on the positive or negative effects of a particular behavior is not enough to cause a change; motivation plays a vital role in enabling that change, which is crucial for the success of the intervention [36]. Hence, APPs shall include attractive, significant contents –based on the context- that motivate patients to use them in a conscious consistent way.

To conclude, at the time of defining the diverse health conditions subject to APP intervention, the vast majority turned out to be chronic diseases. It is acknowledged that patients suffering from chronic disease need a treatment based on highly accurate information, education, management and communication proceedings and therefore APPs are considered as a suitable strategy for favoring communication channels, allowing information to be exchanged in an easy, quick, accessible and comprehensible manner. Two types of intervention were considered: pharmacological and non-pharmacological intervention. This implies that APPs have distinctive features for improving therapeutic adherence. Regarding the pharmacological interventions, 100% of them featured the medication reminder function, 62.5% included educational contents and 25% offered bidirectional communication. Clinical care guidebooks recommend using APPs with reminders to reduce involuntary nonadherence [31, 32]. As for the non-pharmacological interventions, 100% of the APPs included educational contents and cognitive, physical and emotional training. According to Becker et al. [37], non-pharmacological treatments require strategies to change habits and conducts connected to patients' self-care processes. The abovementioned APP functions may be beneficial for caregivers, relatives and health professionals, since the entire social environment improves when patients act in a health-conscious, aware and consistent manner.

Limitations

The use of APPs is an innovation strategy for many patients; however, a limitation may exist with regards to usage. The number of elders using smartphones may be small due to low digital literacy levels, which prevents them from using this kind of mobile tools appropriately. This could also retard the development of new digital strategies, as old adults are the users in need of most of these interventions.

Conclusion

Most of the studies reviewed reported that, in comparison to conventional interventions to increase therapeutical adherence, the strategy involving the use of mobile applications showed a noticeable, and in some cases statistically significant, improvement. The results suggest that the use of mobile applications may be a choice in the professional practice in the future for monitoring treatment, increasing therapeutical adherence, broadening knowledge of the specific condition and improving patient-health professional communication. The mobile application functions that contributed to achieve these goals were: medication reminders, educational items, bidirectional communication, calendars and games. The application of APP interventions to clinical care has proved to be beneficial to improve therapeutic adherence. Nevertheless, it is necessary to develop high-quality clinical trials to generalize about the results and justify its introduction to the conventional health services.

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Author Contribution The evaluation presented here was carried out in collaboration with all authors. BPL developed a study design and supervised the study. EAJC and BP drafted the manuscript. EAJC and BP conducted data collection and analysis. FMR, JLMC, CDF and AMM interpreted results from a medical point of view. EAJC and BP conducted a comprehensive content review. All authors read, revised, and approved the final manuscript.

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Declarations

Ethical Considerations This work does not involve the use of human subjects.

Competing Interest The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results. Sponsor's role: none.

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