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REVIEW

What does the literature say about using electronic pillboxes for older adults? A systematic literature review

Antonio Miguel-Cruz[a,b], Andrés Felipe Bohórquez[a] and Pedro Antonio Aya Parra[a]

[a]School of Medicine and Health Sciences, Universidad del Rosario, Bogotá, Colombia; [b]Department of Occupational Therapy, Faculty of Rehabilitation Medicine, University of Alberta, Edmonton, AB, Canada

ABSTRACT

Purpose: The purpose of this study is to answer two research questions: (1) What is the clinical evidence for the reported outcomes in studies on electronic pillboxes for older adults? and (2) What is the technology readiness level (TRL) of the electronic pillboxes used, or intended to be used, for older adults?

Methods: The scholarly literature was systematically searched and analyzed. Articles were included if they reported results about electronic pillboxes that were used or intended to be used for older adults' medication.

Results: Clinical studies used commercially well-established electronic pillboxes with a high TRL. New electronic pillboxes in development had a low TRL. The discovered outcome was mainly adherence to medication. The overall mean adherence to medication regimens for all the studies using an electronic pillbox was higher than the gold standard of a good adherence level cut-off point (mean adherence 88.8%>80%). However, we found a large variation in this variable ($SD = 10.7$). With regard to an older adult population's adherence to medication regimens, for the outcome variable of those who had undergone a kidney transplant, the clinical evidence that electronic pillboxes have a positive impact *was strong* (1b); for those with a chronic hepatitis C medical condition, the clinical evidence *was medium* (3), and for those with arterial hypertension and multiple chronic (diabetes and hypertension) medical conditions, the clinical evidence *was weak* (5).

Conclusion: More research is needed in this area using designs that provide greater validity.

➤ IMPLICATIONS FOR REHABILITATION

- Electronic pillboxes with multiple reminders such as the "voice of a friend" or relative, which implies that electronic pillboxes which adopt "a social role" are advisable.
- An unequal level of clinical evidence that electronic pillboxes have a positive impact on the adherence outcome variable was found.
- For new electronic pillboxes still in development that specifically take into account older adults' needs, the TRL is still low; as a result, they could not be tested in real settings.

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KEYWORDS
Electronic pillbox; older adults; centered design approach

Introduction

According to a United Nations (UN) report on World Population Ageing, in 2015, the number of people aged 65 or over was approximately 1.05 billion; by 2050, this number is estimated to reach 2.1 billion, which represents a projected growth of almost 100%. The reality that the global population is facing is an ageing population is growing worldwide, not only in developed countries, but also in less-developed countries as well. For example, between 2015 and 2030, the projected growth percentage in the population group aged 60 years or over is nearly identical when more and less-developed countries are compared, i.e., 70% growth for less-developed countries versus 71% growth for developed countries [1].

It is normal for older adults to have chronic medical conditions. They are caused not only by the accumulation of a variety of molecular and cellular damage over time, but also due to changes in social, environmental (retirement, relocation to more appropriate housing) and psychological conditions such as depression, anxiety and the deaths of loved ones [2]. A study conducted in the USA on civilian, non-institutionalized U.S. adults, approximately half (49.8%, 117 million) were affected by at least 1 out of 10 chronic conditions[1] [3]. As people age, they normally have more than one chronic medical condition, which implies that this population would have to take more than one medication. For example, frail older adults with multiple chronic medical conditions have medication regimens according to which they take up to nine different medications on average [4]. A medication regimen is a systematic or structured treatment plan especially designed to improve and maintain a patient's health [5]. Consistent adherence to a specific medication regimen is an important factor in the progression [or not] of a disease. Adherence is defined as when an individual takes his/her medication as prescribed [6]. It has two components, which are compliance and persistence [7]. "Compliance" refers to how much a person's behaviour coincides with the medical orientation

CONTACT Antonio Miguel-Cruz antonio.miguel@urosario.edu.co School of Medicine and Health Sciences, Universidad del Rosario, Calle 63D # 24-31, 7 de Agosto, Bogotá, Colombia

Supplemental data for this article can be accessed here.

regarding a particular medication regimen [8], whereas "persistence" introduces the concept of chronology into the assessment of deviation from treatment recommendations [9]. Some studies have reported that people who are non-adherent range from 20% to 50% [6]. Non-adherence leads to both worse health outcomes for individuals and financial losses in health care. For example, poor medication regimens increase overall hospitalizations by up to 10% [10] and cause up to US $300 billion of avoidable health care costs in the USA annually [11]. As non-adherence to medication is a problem that deserves to be studied, several behavioural and educational interventions have been tested for the improvement of adherence to medication, including: contracts (verbal or written agreements), reminders (charts/medication lists, pillboxes/calendar packs, follow-ups in the form of home visits, scheduled clinic visits, video/teleconferencing) and educational interventions from physicians, pharmacists, nurses, etc. [7]. With the development of electronics and its miniaturization, information and communication technology (ICT), the Internet of things (IoT), the Internet of Everything (IoE) and mobile applications (mApps), it seems that electronics pillboxes and their aids have become an alternative intervention for measuring, monitoring and improving medication regimens. Electronic pillboxes, with their ability to provide systematic medication reminders, pill-dispensing, and assistance strategies through audible and visible alarms using cellphones, tablets, LCD displays, software, etc. are becoming promising assistive devices that can help individuals change their adherence and compliance behaviour. Electronic pillboxes, with their capacity to remind and assist patients, can become part of the "antidote" against the most frequent problem older adults face regarding adherence and compliance behaviour: i.e., "forgetting to take medicine" [12].

To the best of our knowledge, interventions using electronic pillboxes are a way of determining the effectiveness of improving adherence to medication regimens that focus on the elderly population, and so far there have been no systematic reviews of the literature that determine this. In fact, as [13] concluded, there is an acute need for more studies that explore the effects of electronically monitoring patients' adherence to medication. In order to fill this gap, the aim of this study is to provide a comprehensive review that characterizes the state-of-the-art electronic pillboxes used, or that are intended to be used, for monitoring and measuring older adults' medication regimens. The specific research questions of this literature review are:

1. What is the clinical evidence for the reported outcomes in studies on electronic pillboxes for older adults?
2. What is the technology readiness level (TRL) of the electronic pillboxes used, or intended to be used, for older adults?

Method

For this systematic literature review, we followed a review protocol with four main steps: first we determined the search strategy, then we performed the literature search, then we conducted a selection process for relevant articles and finally we extracted the data for our analysis. We included in our study any source of information about electronic pillboxes with at least a TRL 4 or higher, and intended to be used for older adults' medication. In the context of this study, an older adult is understood to be an individual 50 years of age or older. Any study, regardless of its methodology, was included.

Inclusion criteria

1. Any source of information about electronic pillboxes intended to be used for older adults' medication.
   (a) The electronic pillboxes mentioned should be used to assist with medication in any therapeutic intervention in older adults in order to improve their medication regimens.
   (b) Electronic pillboxes are included if they have been implemented or deployed at least as a component and/or breadboard validation in a laboratory environment (TRL 4 or higher).
   (c) Electronic pillboxes are included regardless of their cost.
   (d) The electronic pillboxes developed must be used, or intended to be used, by older adults (individuals over the age of 50).
2. Sources of information include:
   (a) Studies, regardless of their methodology, including research and development, and regardless of the positive or negative nature of their results.
3. Articles/documents are in English or Spanish.
4. Articles/documents from the year 2005 to the present.

Exclusion criteria

1. Studies about electronic pillboxes used, or intended for use, by individuals aged 50 years old or less.
2. Papers that were not available.
3. Full papers that did not provide enough information to categorize the paper (e.g., TRL, ages of the participants).
4. Studies published in books, book chapters, PhD or Master's theses, newspapers, interviews and non-indexed journals.
5. Papers that were lecture notes at conferences, theoretical/seminar papers and any kind of literature reviews.
6. Conference proceedings papers which summarized or commented on a number of papers included in the proceedings book.
7. Studies beyond the scope of this systematic literature review (e.g., genetic, genomic, proteomics, etc.).
8. Studies describing only the components of an electronic pillbox (e.g., sensors, cover mechanisms, software or interface improvements).
9. Any papers studying any other type of dispensing system at the same time were excluded (e.g., papers including robots that dispensed any type of medication).
10. Papers only including a smartphone application controlling an electronic pillbox.
11. Electronic pillboxes only used by health care professionals/practitioners to provide medication for patients, and not by older adults.
12. Electronic pillboxes only used as "measuring instruments" to measure medication regimens in order to determine an association between two variables (e.g., an association between anxiety and non-adherence, level of cognitive impairment and adherence, etc.).
13. Electronic pillboxes only used as "a gold standard of adherence measurement" to determine the validity and reliability of self-reporting adherence/compliance questionnaires.
14. Electronic pillboxes "embedded" as part of a smart home system with the aim of providing full context-aware prompts for the participants when they forgot to take their medication on time (e.g., unobtrusive sensor systems installed in beds, door sensors that collected data from a patient's daily activities).

Information sources. The studies were identified by searching electronic databases. Our search was conducted on the following eight databases: Scopus, Pubmed, Embase, Medline-Ovid, Medline-Ebsco, IEEE Explore, ISI Web of Sciences, Ebsco Host.

Search strategy. Papers were extracted from databases using the following search terms either alone or in combination using the logical operators "AND" and "OR": "electronic", "pillbox", "adherence", "drop-out", "medication", "pill", "drug", "administration", "technology", "older adults", "dispenser", "older", "adult", "aging", "aged", "acceptance", "use", "satisfaction".

First search query 1: (pillbox OR dispenser) AND (electronic OR system OR smart OR technology) AND (adherence) AND (medication OR drug OR pill OR administration OR schedule) AND (adult OR aging OR older OR aged).

Second search query 2: (pillbox OR dispenser) AND (electronic OR system OR smart OR technology) AND (adherence OR compliance OR treatment) AND (medication OR drug OR pill OR administration OR schedule) AND (adult OR aging OR older).

Third search query 3: (pillbox OR dispenser) AND (electronic OR system OR smart OR technology) AND (non-adherence OR drop-out OR adherence) AND (medication OR drug OR pill OR administration OR schedule) AND (adult OR aging OR older OR elderly).

Fourth search query 4: (pillbox OR dispenser) AND (electronic OR system OR smart OR technology) AND (medication OR drug OR pill) AND (use OR acceptance OR satisfaction).

Study selection. For this study's selection phase, we followed a variation of Liu et al.'s [14] and Miguel-Cruz et al.'s [15] procedures, including: first, a database search and initial removal of duplicates carried out by one researcher (PAAP). Second, two pairs of independent raters (a researcher with a research assistant) (pair 1: PAAP and VC; pair 2: AFBH and NSR) that evaluated the titles and abstracts of the remaining articles, and compared them with the inclusion and exclusion criteria. Each pair of raters met to reconcile any differences through discussion. If there was any disagreement on the suitability of a paper's abstract, the abstract was included in the next phase. Third, the two pairs of raters reviewed the full texts of the selected papers. Each researcher independently assessed all of the papers to determine their suitability for inclusion in the data extraction phase. In case of any disagreement regarding the suitability of a paper, a fifth rater acted as a third rater making a final decision about whether or not to include that paper in the data extraction phase [the main author (AMC) acted as a third rater for any disagreement in either pairs 1 or 2]. In 3.0% of cases (2/64 papers), the third rater had to make a final decision about whether or not to include that paper in the data extraction phase.

The data collection process. For the data extraction phase, two pairs of independent raters (a researcher with a research assistant) (pair 1: PAAP and VC; pair 2: AFBH and NSR) completed the data extraction on all of the final selected papers, and annotated the operationalization of the variables in an Excel spreadsheet file. Finally, as a test of the validation of the data extraction, the main author (AMC) reviewed all of the selected articles and all the variable operationalizations saved in the Excel spreadsheet file. In case of any disagreement regarding the extracted information, one of the researchers acted as a third rater making a final decision about what information was to be included in the Excel spreadsheet file. We ensured that this third rater did not review the same paper which he/she had performed a data extraction on.

Data items. Each selected paper was carefully reviewed and the data were extracted for the following attributes:

Bibliometric indicators of the publication: The journal's name, the year of the study's publication, the authors' country of affiliation, the source-normalized impact factor per paper (SNIP, according to Scopus) and the type of publication (peer-review or conference paper).

Characteristics of the research conducted with electronic pillboxes

Participants. The participants' ages and gender distribution (as a %), as well as the type of diagnosis (i.e., arterial hypertension, kidney transplant, multiple chronic conditions, including diabetes and arterial hypertension, chronic hepatitis C and heart failure).

Characteristics of the research conducted with electronic pillboxes. The sample size, the length of the experiment (in years/months/weeks), the number of sessions, the sessions' duration (minutes/hours), the type of topic or problem undertaken (i.e., technology-oriented studies, clinical-oriented studies, usability or a combination of these), the design of the study according to [16] for qualitative research, i.e., phenomenology, ethnography, grounded theory, participatory research action (PAR), etc., and according to [17] for quantitative research, i.e., randomized control trial (RCT), cohort, single case design, pre-test post-test no control group, pre-test post-test with control group, post-test-only control group, case control, cross-sectional and case study; for the technology-oriented studies, we used "technology development" as the study design, the setting where the electronic pillbox was tested (i.e., laboratory, hospital/rehabilitation center, school, home, other), the type of outcome variables by diagnosis (see below), a description of the main outcomes of the study, the sizes of the effects of the main outcomes variables (if reported) and the quality of the studies (measured according to the Physiotherapy Evidence Database (PeDro) Scale [18]).

Type of outcome variables. We extracted the outcomes (i.e., adherence, compliance, acceptance, etc.) reported in the papers for each diagnosis (i.e., arterial hypertension, kidney transplant, multiple chronic conditions, including diabetes and arterial hypertension, chronic hepatitis C and heart failure).

Technical features of the electronic pillboxes used in the study. We used the technical features proposed in reference [19] to extract the technical features of the electronic pillboxes used in the study, including the general features of the electronic pillboxes, number of compartments, type of shape (i.e., circular, rectangular, etc.), communication systems between the electronic pillboxes and the accessories (e.g., cellphones, tablets, wristbands, etc.) used and software and hardware interfaces.

Technology readiness level (TRL) of the electronic pillboxes used in the study. This was measured by an indicator that assesses the maturity of evolving technologies during their development and early operations. We used a technology readiness scale from the U.S. Department of Energy [20], where nine levels are used; TRL1, where the basic principles of technology are observed and reported, and TRL9, where the system is in full operation (i.e., the actual system operates over the full range of the expected mission conditions).

Level of clinical evidence of the studies. We assessed the levels of clinical evidence for each diagnosis addressed (i.e., arterial hypertension, kidney transplant, multiple chronic conditions, including diabetes and arterial hypertension, chronic hepatitis C and heart failure) and the outcomes. We used an adaptation of

Table 1. Levels of evidence.

Levels of evidence	Number of RCT	PeDRO Scale score	Additional characteristics
1a	More than one	6 or higher	Includes within subjects comparison with randomized conditions and crossover designs.
1b	One	6 or higher	
2	One	6	**Non-RCTs** and **Cohort studies** (using at least 2 similar groups with one exposed to a particular condition).
3	N/A	N/A	**Case-Control**: a retrospective study comparing conditions, including historical controls.
4	N/A	N/A	**Case Series**: retrospective chart review. **Pre-Post**: A prospective trail with a baseline measure, intervention and a post-test using a single group of subjects. **Post-Study**: a prospective post-test with two or more groups intervention. Post-test using a single group of subjects.
5	N/A	N/A	**Observational** studies using **cross-sectional** analysis to interpret relations: **clinical consensus**, expert opinion without explicit critical appraisal or based on physiology, biomechanics or "first principles": or **Case Report, pre-pose or case studies** ($n = 1$)
Conflicting	N/A	N/A	• Absence of evidence: agreement by a group of experts on the appropriate treatment course. • Disagreement between the findings of at least two RCTs. • Where there are more than four RCTs and the results of only one was conflicting, the conclusion was based on the results of the majority of the studies, unless the study with conflicting results was a higher quality

the modified Sackett criteria proposed by Teasell et al. [21] in order to summarize the findings (see Table 1 for more detail).

Bias control

Control bias across the studies. We avoided bias across the studies, including source bias [22] (i.e., by searching in a variety of source databases); publication bias [23] (i.e., by including papers with positive and negative results); bias resulting from studies' low conceptual and methodological rigour [24] (i.e., by including papers registered in electronic abstract systems); Tower-of Babel bias [25] (i.e., by including Spanish papers and excluding non-English papers from our sample, which represented only 0.38% of the total (Turkish 0.08% (1/1320), French 0.30% (4/1320)); rater bias (i.e., by including two pairs of raters during the selection process for relevant articles); and bias overestimating the conclusions in the analyzed papers (i.e., by extracting the information from both the outcomes and on how they were measured).

Control of bias in individual studies. For RCT studies, the risk of bias in individual studies was measured using the Physiotherapy Evidence Database (PeDro*)* Scale [18]. For non-RCT studies, we used available standards and recommendations for critical reviews as an assessment proxy of the risk of bias in these studies [16,17,26].

Results

Study selection. The database search (see Figure 1) provided a total of 1320 citations. After adjusting for duplicates, a total of 386 studies remained. Of these, 322 studies were discarded, because after reviewing the abstracts and titles these papers clearly did not meet the inclusion criteria. The full texts of the remaining 64 citations were examined in more detail. Forty-two studies did not meet the inclusion criteria as described. Twenty-two studies were finally included in this review.

The level of agreement between the raters was 95.2% average agreement for the abstracts, and 96.0% average agreement for the full papers (see the flow diagram in Figure 1 for more detail).

Bibliometric characteristic of the journals and papers included. Most of the included studies, 68% (15/22), were journal papers (see Figure A.1. in the Supplementary material for more detail). The trend for the number of studies per year is shown in Figure A.2. in the Supplementary material; a clear upward trend in the number of published papers over the years can be observed. Overall, the studies published in journals were characterized by a low normalized impact factor (i.e., SNIP mean 1.0 SD 0.5) and were located mostly in the Q1 and Q2 journal quartiles (i.e., 59% (13/22)) [27]. More than a third of studies were conducted in the USA 36.4% (8/22); 13.6% (3/22) of the cases were international collaborations (see Figure A.3. in the Supplementary material).

Characteristics of the included studies (general). Table 2 shows a summary of the included studies characterizing the number of studies, the types of electronic pillboxes used and their mean TRL ± SD, the main features used to describe the participants, the studies' designs, the level of evidence of outcomes and the types of study per medical condition.

Studies per diagnosis. In general, 45.5% (10/34) of the studies did not report a medical condition, mainly because these studies were devoted to showing new designs of and uses for electronic pillboxes (70%, 7/10). Nine studies, 40.9% (9/22), used electronic pillboxes as an intervention to improve the outcomes related to medication adherence in older adults with either arterial hypertension (13.6%, 3/22), kidney transplant (13.64%, 3/22) or multiple chronic conditions (13.6%, 3/22), whereas 13.6% (3/22) were devoted to studying interventions by electronic pillboxes on participants with either chronic hepatitis C (4.6%, 1/22), heart failure (4.6%, 1/22) or osteoporosis (4.6%, 1/22).

Participants. In total, the studies included 2396 participants, who were characterized by high variations in sample sizes (mean sample size 342.3 ± 523.0, maximum sample size =1489; minimum sample size =21). Among the included studies that reported the participants' demographics, there was a gender distribution of 50/50 (i.e., male/female), with an overall mean age of 65.1 ± 3.9. The studies with higher numbers of participants were those with arterial hypertension (1489), kidney transplant (350) and multiple chronic conditions (326), comprising 90.4% of the participants (2165/2396).

Methods (study designs). In general, the studies used a quantitative approach 68.2% (15/22) with weak research designs. We found only 13.6% RCT studies (3/22) in our sample. In addition, the RCT studies were rated with a mode of 4 measured according

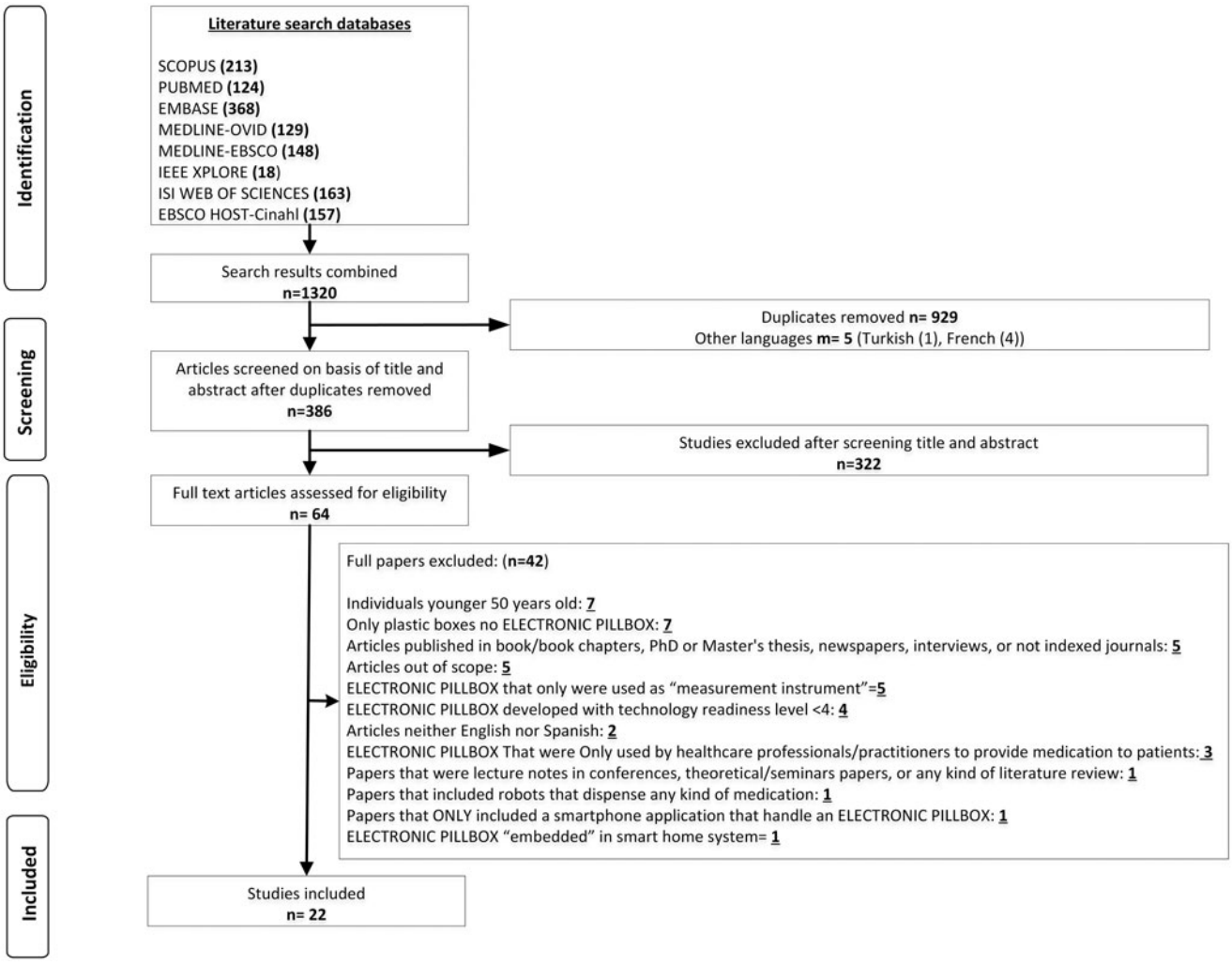

Figure 1. Scholarly reviewed literature article search results.

to the PeDro Scale. The remaining studies were mostly cross-sectional 36.4% (8/22). There was only one pre-test-post-test study with a control group (4.6%, 1/22), one case study (4.55%, 1/22), one phenomenology study (4.6%, 1/22) and one study that used a mixed approach (4.6%, 1/22).

Settings. The studies were conducted mostly either in the participants' homes or in hospitals/rehabilitation centers for 45.5% of the cases (10/22). A small proportion of the studies were conducted at either universities or research centers in laboratory settings 13.6% (3/22). The settings were not reported in 40.9% (9/22) of the cases.

Interventions. In general, the interventions took an average of 24.2 ± 20 weeks (i.e., 6 ± 5 months), minimum= 24 weeks, maximum= 92 weeks. The aims of the clinical study interventions can be classified into three main streams. One intervention stream intended to determine whether an electronic pillbox compared with a standard of care improved the outcome variable under study (e.g., adherence, compliance) [13,34,45,46]. Another intervention stream aimed to determine whether an electronic pillbox with and without an alarm reminder system improved the outcome variable under study (e.g., adherence, compliance) [35]. Another type of "intervention" was to monitor the participants' medication regimens in order to determine how an electronic pillbox improved the outcome variable (e.g., adherence, compliance, impact of adherence on blood pressure), [37,39,41,47]. The standard of care is understood to be a reminder system (chart/medication list, plastic non-electronic pillbox/calendar pack, follow-up by means of home visits, scheduled clinic visits, video/teleconferencing) or educational interventions provided by a physician, pharmacist, nurse, etc. [7].

Outcomes. Table A.1 in the Supplementary material shows a summary of the included studies evaluating the results per outcome variable for arterial hypertension, kidney transplant, multiple chronic conditions, chronic hepatitis C, heart failure and osteoporosis diagnoses. Adherence and compliance were the most common outcome variables used, in 60% of the cases (9/15); user acceptance of the electronic pillboxes occurred in 40% (6/15) of the cases. In all the studies, adherence was calculated as the (total number of doses taken correctly)/(total number of doses prescribed) $\times$ 100% within a specific time interval. Overall, the mean adherence for all the studies using an electronic pill box was higher than the gold standard of good adherence levels (+80%), but with a large variation, i.e., 88.8 ± 10.7. Different dimensions of the adherence outcome variable were used in order to obtain a better characterization of the medication regimens. These variables were: the difference in overall adherence (when the overall

Table 2. Summary of the included studies evaluating the level of evidence per diagnosis (clinical-usability studies, $n = 22$).

		Electronic pillbox		Participants					
Medical condition or diagnostic	Total studies (%)	Types of Electronic Pillbox (number of studies)	Mean TRL ±SD	*N*	Age mean ± SD	Gender M/F	Design of Study/PeDro[g] (number of studies)	Types of results	Study
Undetermined	10 (45.5)	Medication Event Monitoring System (MEMS)[b] (5) PROMES (1), e-Pill CASIO® (1), MedTracker(1), Dyn-e-Pill (1), SMIPLUS(1)	5.6 ± 1.9	84	71.9 ± 47.5	43/45	New development (7) Phenomenology (1) Cross sectional (2) Case study (1)	Positive (66.6%) Mixed (0.00%) Negative (33.3%)	[28,29,10,26,30–35]
Arterial Hypertension	3 (13.6)	MedSignals[a] (1) Helping Hand Medical Device (1) Medication Event Monitoring System (MEMS)[b] (1)	9 ± 0	1489	61.6 ± 6.0	721/768	Cross-sectional (3)	Positive (33.3%) Mixed (0%) Negative (66.7)	[36,37,38]
Kidney transplant	3 (13.6)	MEMS®-V Track- Cap system[c] (1) The Helping Hand™ [h](1)	8.7 ± 0.57	350	55.5 ± 15.9	203/147	RCT (1)/PeDro = 4 Cross-sectional Correlational (1) Mixed. Cross-sectional (1)	Positive (33.3%) Mixed (33.33%) Negative (33.3%)	[39,33,40]
Multiple chronic conditions[d]	3 (13.6)	MD.2 Medication Dispenser (1) Medical Event Monitoring System, MEMS (1)	8.3 ± 1.2	326	71.4 ± 9.1	161/165	Cross-sectional (2) Before–After with control group (1)	Positive (33.3%) Mixed (33.33%) Negative (33.3%)	[41,42,43]
Chronic hepatitis C	1 (4.6)	Sensemedic[e] (1)	9 ± 0	68	50 ± 9.0	52/16	RCT (1)/PeDro = 4	Mixed (100%)	[44]
Heart failure	1 (4.6)	MedSignals (1)	9 ± 0	58	69 ± 11	18/40	RCT (1)/PeDro = 6	Mixed (100%)	[45]
Osteoporosis	1 (4.6)	Medical Event Monitoring System, MEMS[b]	9 ± 0	21	76 ± NR[b]	0/21	Longitudinal, observational study	Negative (100%)	[17]

[a]MedSignal Vital sings LLC, http://www.medsignals.com/; [b]Generic, not reported the original equipment manufacturer; [c]Evalan BV, https://evalan.com/; [d]Diabetes, Arthritis, Hypertension and COPD; [e]WestRock Company, http://www.medamigo.com/products/mems-cap; [f]AARDEX,Ltd; [g]PeDro scale for measuring RCT quality [20]; [h]Bang & Olufsen Medicom, http://www.medicomip.com/home/.

Table 3. Summary of the included studies on new technological developments ($n = 7$).

Architecture	Total studies (%)	TRL	General features of the pillbox	# Compartments	Shape	Communication system	Software interface	Hardware	Study
Electronic Pillbox + mobile devices (e.g., cellphones, tablets)	3 (13.6)	4	**Control server** (communication between the pillbox and central station and medication recording) **Client (the electronic pillbox)** Audible and visible alarms (SMS texts) reminders to a cellphone Programmable functions	14	Circular	RS232 Bluetooth Cellphone, SMS message)	Executable file programed in Lab Windows	Microcontroller ATmega128L Hall Effect sensor Lithium battery (4.2 V)	[26]
		5	**Control server**. Web platform for (communication between the pillbox and central station and medication recording functions) **Client (the electronic pillbox).** Medication reminding, pill-dispensing, assisting Audible and visible alarms (SMS texts) reminders to a cellphone and Tablet Programmable functions LCD display	14	Circular	Bluetooth and WIFI	NR	Microcontroller Storage information Module (SD card) Rechargeable battery	[34]
		4	**Control server.** (Communication between the pillbox and wristband and central station via RFID. Medication recording functions) **The clients** 1. **Wristband** (receives server reminders). Reminding functions 2. **Electronic Pillbox.** Medication reminding, pill-dispensing, and assisting functions. Has audible and visible alarm reminders sent to a wristband, the compartment lid opens and closes automatically when the user takes the pill	7	Circular	RFID ZigBee transceiver	LabVIEW (National Instrument, Austin, Texas, United States) MATLAB (MathWorks, Natick, Massachusetts, United States)	**Wristband:** Arduino LilyPad board + ATMega328 microcontroller, MPU-9150 chip + a tri-axis accelerometer, gyroscope and a tri-axis compass **Electronic Pillbox:** Arduino Fio, ATMega328P, Mercury Motor SM-42BYG011-25, RFID reader 16MHz, photodiode and a diode)	[10]
		4	**Electronic pillbox.** Medication reminding, pill-dispensing, assisting Audible and visible alarms (SMS texts) reminders to Tablet Programmable functions LCD display	3	NR	HC-06 Bluetooth	Arduino IDE, Android SDK, Python 2.7 and Plotly Library	Arduino Uno Tilt sensor 3 Servo motors and direct current motors	[35]
Electronic Pillbox alone or Electronic Pillbox + Computer	4 (18.2)	5	**Master panel (MP).** Serves as network gateway/database as well as the charging dock for the SPBs registered under the MP **Smart pill-boxes (SPBs)**. Medication reminding, pill-dispensing, assisting, and medication recording	7	Rectangular	RF chip which complies with the ZigBee/IEEE 802.15.4		RF transceiver chip (UZ2400, UBEC® Microcontroller chip (MSP430F1611, Texas Instruments® Three-state magnetic pill-detection magnetic sensor (MMC212Xmg, MEMSIC)	[29]
		4	Detection (monitoring the users' position and the medication), inference (informing, guiding, and warning functions), and actuation modules (assists the users with pill taking).	15	Rectangular	NR	NR	Ultrasonic sensors	[30]
		6	**Electronic Pillbox.** Medication reminding, pill-dispensing, and assisting functions.	7	Rectangular	Bluetooth	NR	18LF252 PIC microcontroller Blue Stamp BR-SC30A 9V battery	[31]

adherence during the follow-up period minus the overall adherence during the baseline period exceeded 20%), stable adherence (when the adherence for each study month did not exceed a 10% difference from the mean adherence of the whole study period), non-persistence (gaps in the use of a medication of 30 days or more), dosing adherence (the percentage of days with the correct dosing), timing adherence (the percentage of inter-dose intervals within 25% of the prescribed interval) and drug holidays.

There is general agreement between scholars regarding setting up cut-off points of 80% and 100% for good and perfect adherence, respectively. Only in 20% of cases were the physiological or clinical variables used as an outcome variable to determine whether electronic pillboxes were having an impact on these users' health outcomes (i.e., systolic and diastolic blood pressure, plasma ribavirin levels, virological responses of the participants). None of the studies that used an electronic pillbox as a strategy to improve the participants' adherence and medical conditions obtained positive results.

User acceptance was measured by either five- or four-point Likert scale questionnaires enquiring about aspects such as ease of use and general user satisfaction. Studies on smart pillbox users showed higher levels of user acceptance.

Types of electronic pillbox used and their TRL. Seventeen electronic pillbox systems reported in 22 studies were found, i.e., 7 newly developed and 10 well-established electronic pillbox brands. The clinical and usability studies used the 10 commercially well-established electronic pillboxes with a high TRL (i.e., TRL mean 8.9 ± 0.3, TRL mode $=9$). For the electronic pillbox brands used, see Table 1 for more detail. For the new electronic pillboxes in development, 31.2% (7/22) of the cases had a low TRL (i.e., 5.6 ± 1.9); as a result, they have rarely been tested in real contexts with older adults. Two main generic types of new electronic pillboxes have been devised; those that are electronic pillboxes plus a remote computer system in order to follow the users' adherence to their medication regimens, 42.9% (3/7); and those that use an electronic pillbox in combination with mobile applications installed in either tablets or smartphones to improve reminders of and assistance with adherence to medication regimens. For the electronic pillboxes' general features, their numbers of compartments, shapes, communication systems and software and hardware interfaces, see Table 3 for more detail.

Characteristics of the individual included studies (outcomes)

Level of evidence (positive, negative and mixed results). We found that 33. 3% (5/15) of the clinical and acceptance studies had positive results in their outcome variables (in favour of what the author had expected), 40% (6/15) had negative results and 26.7% (4/15) of the studies had mixed results. Therefore, almost 70% of the studies that aimed to either determine the impact or acceptance of electronic pillboxes on adherence had either negative or mixed results.

Level of evidence of outcomes: adherence per medical condition. Although the overall mean adherence to medication regimens for all the studies using an electronic pillbox was higher than the gold standard of a good adherence level cut-off point (i.e., mean adherence 88.8% $>$ 80%), we found a large variation in this variable (i.e., $SD = 10.7$). This suggests that the adherence variable range was from 78% to 98%, and in some cases a lower level than the gold standard of adherence was obtained.

With regard to the outcome variable of adherence to medication regimes of older adults who had undergone a kidney transplant, the clinical evidence that electronic pillboxes have a positive impact ***was strong*** (ranked **1b** according to [21]). There was one RCT [45], which rated 8 according to the PeDro Scale. This study demonstrated that the use of electronic pillboxes was associated with higher levels of adherence (i.e., 97.8 $\geq$ 80%). There was also a cross-sectional study with positive results, where the adherence was 98.4 ± 5.1 [37], a value higher than the accepted gold standard of good adherence.

With regard to the outcome variable of adherence to medication regimes of older adults with a heart failure medical condition, the clinical evidence that electronic pillboxes have a positive impact on medication regimes ***was strong*** (ranked **1b** according to [21]). There was one RCT [34], which rated 6 according to the PeDro Scale. This study demonstrated that the use of electronic pillboxes had levels of adherence to medication regimes higher than the good adherence cut-off point (i.e., 82 $\geq$ 80%), although the type of intervention device (i.e., an electronic pillbox versus Telehealth, Smartphone, passive medication) was not significantly associated with medication adherence ($p = 0.87$).

With regard to the outcome variable of adherence to medication regimes of older adults with a chronic hepatitis C medical condition, the clinical evidence that electronic pillboxes have a positive impact ***was medium*** (ranked **3** according to [21]). There was one RCT [35], which rated 4 according to the PeDro Scale. This study demonstrated that the use of an electronic pillbox was associated with higher levels of adherence (i.e., 96% $\geq$ 80%), although the reminder systems in the devices did not influence adherence ($p \geq 0.05$).

With regard to the outcome variable of adherence to medication regimes of older adults with an arterial hypertension medical condition, the clinical evidence that electronic pillboxes have an impact ***was weak*** (ranked **5** according to [21]). We assert that this was because none of these three articles incorporated RCT designs or a control group. The two papers which assessed adherence were observational studies using cross-sectional designs with negative results. One study obtained overall adherence values below the gold standard cut-off adherence value (i.e., 75.4 $\langle$80%) [41], whereas the other study failed to demonstrate that the use of an electronic pillbox was a better method for improving adherence compared to the refill method [13].

With regard to the outcome variable of adherence to medication regimes of older adults with multiple chronic medical conditions (diabetes and hypertension), the clinical evidence that electronic pillboxes have no impact ***was weak*** (ranked **4** according to [21]). There was one before/after with control group study, which, although it showed that the mean adherence to a medication regimen using an electronic pillbox was higher than the gold standard of a good adherence level cut-off point (i.e., adherence ranging from 94.5 to 98.4% $>$ 80%), this study failed to find statistically significant differences in adherence between the intervention (an electronic pillbox as an intervention) and the control group (standard care) ($p = 0.31$) [46]. Another study [39] used a cross-sectional design which found positive results where the adherence was greater than the gold standard of good adherence (88% $>$ 80%).

With regard to the outcome variable of adherence to medication regimes of older adults with an osteoporosis medical condition, the clinical evidence that electronic pillboxes have no impact ***was weak*** (ranked **5** according to [21]). There was one study where the adherence was insufficient (around 70%) at the baseline and at the follow-up, and the adherence did not change significantly between the months ($p > 0.05$) when the users were utilizing an electronic pillbox [42].

Level of evidence of outcomes: the effect of electronic pillboxes on physiological or clinical variables according to medical conditions. The clinical evidence that electronic pillboxes have a positive impact on the adherence outcome variable, but not on the physiological or clinical variables for older adults with a kidney transplant medical condition, ***was strong*** (ranked **1b** according to [21]). There was one RCT [45], which rated 8 according to the PeDro Scale, and which found that although biopsy-verified rejection was three times more common among controls compared with intervention groups (medication using an electronic pillbox), it was thus not statistically significant ($p > 0.05$). The same was true for the average p-creatinine level, which was slightly lower in the intervention group compared with the control group, but not statistically significant ($p > 0.05$).

The clinical evidence that electronic pillboxes have a positive impact on the adherence outcome variable, but not on the physiological or clinical variables for older adults with a chronic hepatitis C medical condition, ***was medium*** (ranked **3** according to [21]). There was one RCT [35], which rated 4 according to the PeDro Scale. This study found that the levels of ribavirin and virological responses did not differ between the intervention (using an electronic pillbox) and control groups (standard of care) ($p = 0.69$).

Finally, the clinical evidence that electronic pillboxes have a positive impact on the adherence outcome variable, but not on the physiological or clinical variables for older adults with multiple chronic medical conditions, ***was weak***. One study [39] used a cross-sectional design that found no evidence to suggest that adherence was associated with lower values of systolic blood pressure (SBP), and there was no difference between baseline systolic or diastolic blood pressure (DBP) before and after using an electronic pillbox (SBP 145 mmHg vs. 148 mmHg, $p = 0.46$; DBP 83 mmHg vs. 82 mmHg, $p = 0.57$).

Discussion

This systematic review of the literature answered two research questions: (1) *What is the clinical evidence of the reported outcomes in studies on electronic pillboxes for older adults?* and (2) *What is the technology readiness level of electronic pillboxes used, or intended to be used, for older adults?* In doing so, we provided a different point of view regarding the use of electronic pillboxes for older adults from previous literature reviews which aimed at either reviewing the types of interventions (a combination of educational and behavioural interventions) [7], or reviewing the different components of the interventions' designs, interventionist training, delivery, receipt, etc. for improving adherence to medication [6,38,44]. In doing so, we carried out a critical and comprehensive review of studies in order to identify the clinical evidence of their reported outcomes, and to identify the TRL of the electronic pillboxes (both established and newly developed brands) used in the studies. These are the main contributions of this systematic review of the literature.

We found that the evidence pertaining to the improvement of adherence to medication regimes using electronic pillboxes varied according to the medical conditions. Adherence to medication improved for users who had undergone a kidney transplant and were in heart failure, but for other medical conditions such as diabetes and hypertension, the evidence that using electronic pillboxes improved adherence was still weak. These results are consistent with other reviews where the authors were unable to conclude from the evidence that electronic pillboxes had an impact on improving adherence to medication with regard to any particular intervention and/or medical condition [7,36]. The differing evidence that electronic pillboxes had an impact on adherence to medication with regard to each medical condition can be explained by the disparity in the numbers and quality of the studies found for each medical condition. We found RCTs in studies with some medical conditions, while in other studies no RCTs were found.

The discussion between scholars in this field continues the debate on the use of medical pillboxes with regard to adherence to medication regimes. One argument stipulates that an improvement in adherence to medication does not equate to an improvement in the patient's condition. Therefore, it is desirable that electronic pillboxes not only improve adherence, but that they also help to improve the medical conditions of the patients who are taking the medication. However, we found little evidence that electronic pillboxes have a positive impact *per se* on the improvement of variables such as blood pressure, etc. due to an improvement in adherence. It is logical to think that factors other than medication regimens influence improvements in patients' medical conditions, although we cannot explain what causes this result because it has not been reported in other studies.

We found that, in general, although with large variations, interventions using electronic pillboxes to improve adherence to medication regimens were on average 24.22 weeks (i.e., 6 months).

We found that the mean adherence to medication regimens for all the studies using an electronic pillbox was higher than the gold standard of a good adherence level cut-off point (i.e., mean adherence 88.8% > 80%), but with large variations in this outcome variable (i.e., a standard deviation of more than 10 points, $SD = 10.65$). This large variation can be explained by the fact that well-established electronic pillbox brands do not have specific designs that meet the needs of older adults. For example, scholars have reported that about 20% of elderly patients cannot use these devices due to obstacles such as impaired dexterity, vision or cognition [28]. Unfortunately, the electronic pillboxes designed with specific purposes for the population group in this review could not be tested in real settings due to their low TRLs.

Implications for practice and future research

Most electronic pill boxes' geometries, either those already established on the market or still in the development process, were found in our study to have lots of small compartments (up to 15 compartments, see Table 3 for a summary of the included studies on new technological developments), thus making it hard for older adults to take their medications out of them. Therefore, from a technological point of view, a centred user design approach is needed to develop new electronic pillboxes for older adults. We recommend that developers use this approach. In addition, the participation of interdisciplinary teams in the design, development and implementation of new electronic pillbox systems is of extra value. Developers of new electronic pillboxes should take into account that people over the age of 60 have special needs and most of them have multiple chronic medical conditions and disabilities. For example, they are not able to learn or remember how to use these systems; at the same time, they might have severe hearing limitations and cognitive problems [43]. Therefore, electronic pillboxes with multiple reminder strategies on how to take medication are useful. Other strategies include audio feedback using the "voice of a friend" or relative, which implies that electronic pillboxes which adopt "a social role" are advisable. Developers should also pay special attention to the design and implementation of the storage and dispensing boxes

of electronic pillboxes for older adults. As older adults in some cases might have arthritis, taking the medication out of the dispensing pill tray/opening/drawer could be difficult for them. Therefore, special care should be taken when designing the size/capacity of the pill tray/opening/drawer; they should be adequate, and the medication must be secure and not become lost/fall out. At the same time, the user should be able to open and close the device easily.

The dispensing mechanism should not be confusing for older adults. We found that almost 50% of electronic pillboxes are used in combination with mobile applications installed in either tablets or smart phones to improve the reminding of and assistance with adherence to medication regimens. Although these new developments of electronic pillboxes that use mobile applications such as a personal digital assistant (PDA), which can be installed on tablets and smartphones to facilitate the management of medication regimens can be useful, for the specific case of older adults, developers should take into account that older adults might run into difficulties with how to use these types of devices. For example, in a study with the aim of determining the usability of an electronic pillbox with a PDA to manage medication for older adults, after 9 h of training only 25% of the participants were able to demonstrate complete mastery of the PDA [48]. Thus, during the devices' deployment phases, providers should take into account the cost of training and follow-up. For older adults, developers should take the time to design easy checklists that teach them how to use these devices. The cost of some electronic pillboxes can be as much as US$199.00, which is still too high to be implemented in most homes of older adults in low-income countries. Thus, we recommend the design and development of low-cost electronic pillbox systems in order to make them more affordable.

From a clinical perspective, researchers and developers should take into account that the use of electronic pillboxes to improve adherence to medication regimens should not be viewed as a *panacea*. Previous review studies on medication adherence [38,44] showed that clinical interventions with better results regarding medication adherence involve a combination of using electronic pillboxes with other strategies such as dosage simplification or combinations of counseling, reminders, follow-ups, supervised self-monitoring and feedback. Very few RCTs were found with low PeDro Scale values, which means that more research should be conducted into these topics. Finally, as medication adherence is an individual's self-regulatory process, we encourage researchers to conduct more research in order to better understand the mechanisms that underlie the self-regulation, self-influence, self-monitoring, self-judgment and self-reinforcement of adherent and non-adherent behaviours, in turn to implement better strategies to improve adherence to medication regimens in the older adult population.

Study limitations

Our reviews have some limitations. First, it is possible that not all the relevant studies were identified, because we designed a search strategy to minimize the number of irrelevant studies. In addition, although we used a thorough search strategy, some empirical studies on the use of electronic pillboxes by older adults may not have been identified for this review (e.g., the grey literature such as unpublished documents and reports), because we only included papers that had been published in peer-review journals and conference proceedings. Second, conducting a meta-analysis in this review was impossible due to the diversity of the study designs and outcome measures we found there. Most of the designs were cross-sectional studies with no control group condition, which did not meet the standards for adequate internal validity. This increased the risk of bias towards the included studies. Third, there were a number of parameters during the data extraction phase that could not be examined because the papers did not report them, including the older adults' medical conditions, features of the electronic pillboxes and the settings where the experiments were conducted. Therefore, Bartlett-Ellis et al.'s suggestion [6] that studies on pillboxes to improve adherence in older adults should provide as many details as possible in order to increase their fidelity is still valid (fidelity in their design, training, delivery, receipt and enactment). Finally, we did not include wildcards in our search strategy (e.g., dispenser*, old*, etc.); therefore, some relevant studies may have been omitted from our literature review.

In conclusion, 17 electronic pillbox systems reported in 22 studies were found, i.e., 7 newly developed and 10 well-established electronic pillbox brands. For the 10 well-established electronic pillbox brands, we found an unequal level of clinical evidence that these electronic pillboxes have a positive impact on the adherence outcome variable. However, for some medical conditions, the clinical evidence that electronic pillboxes have a positive impact on the adherence outcome variable was strong (kidney transplant and heart failure medical conditions); for other medical conditions, the clinical evidence was either medium or weak (diabetes and hypertension). For new electronic pillboxes that were still in development and that specifically took into account older adults' needs, the TRL was still low; as a result, they could not be tested in real settings. A large variation in the adherence outcome variable was found (i.e., high standard deviation $SD = 10.65$). Therefore, more research is needed in this area using designs that provide greater validity.

Note

1. Hypertension, coronary heart disease, stroke, diabetes, cancer, arthritis, hepatitis, weak or failing kidneys, current asthma or chronic obstructive pulmonary disease [COPD]

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The authors Antonio Miguel-Cruz, Andrés Felipe Bohórquez and Pedro Antonio Aya Parra declare that they have no conflicts of interest.

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