



Technological Innovations in Medication Packaging to Improve Patient Adherence: A Systematic Review

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Abstract

Importance: Nonadherence to medications affects over one in four patients in the US, reaching as high as 50% for many chronic drug regimens. One strategy to combat nonadherence may be improved use of electronic medication packaging (EMP) devices built into the containers through which pills, inhalers, or other products are dispensed.

Objective: To investigate whether EMP devices are effective in reducing medication nonadherence, identify common features of successful EMP devices, and assess the potential for this tool to reduce adverse outcomes related to nonadherence.

Evidence Acquisition: Peer-reviewed research testing the effectiveness of electronic medication packaging was identified using a systematic literature search. The results describing the impact of the interventions on adherence as well as other key findings were extracted, and each study was formally assessed for bias using the guidelines outlined in the Cochrane Handbook for Systematic Reviews of Interventions. Finally, the devices described in each study were evaluated qualitatively in order to determine common features of EMP devices that may affect adherence outcomes.

Results: A total of 37 studies met review criteria: 10 patient-interface-only “simple” interventions and 29 studies of “complex” interventions (2 qualified for both categories) in which the EMP devices were linked to care delivery by a physician, pharmacist, or other caregiver. Few studies of simple EMP interventions (3/10, 30%) improved medication adherence. By contrast, complex EMP interventions demonstrated improved adherence in a majority of studies (20/29, 69%). My qualitative review identified 5 prominent characteristics of EMP interventions: recording dosing events and storing a record of adherence, audiovisual reminders to cue dosing, digital displays, real-time monitoring, and providing patients with adherence performance feedback. Recording dosing events, digital displays, and providing feedback were most frequently found in studies that led to improved medication adherence.

Conclusion and Relevance: This systematic review found that EMP devices can significantly improve medication adherence, particularly those that are integrated into the care delivery system and that are designed to record dosing events to give the opportunity for feedback. Well-designed EMP devices can help physicians and patients seeking strategies to promote medication adherence.

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Glossary of Abbreviations:

EMP, Electronic Medication Packaging

HIT, Health Information Technology

HIV, Human Immunodeficiency Virus

IQR, Interquartile Range

PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses

US, United States (of America)

Introduction

Medication nonadherence is a common and increasingly recognized problem in health care delivery.^{1,2} Under-use of prescribed drugs affects over one in four patients with hypertension, hyperlipidemia, and diabetes in the US.³ Non-adherence has been linked to important adverse health effects including stroke in hypertensive patients, higher viral load in patients with HIV, and hospitalization and mortality in patients with heart failure.⁴⁻⁶ It has been estimated that approximately 125,000 deaths occur annually as a result of nonadherence.⁷ The cost to the US health care system may exceed \$300 billion per year from complications that could have been prevented if patients had taken their medications as prescribed.⁸

Medication nonadherence is also common in resource-poor settings.⁹ The World Health Organization estimated in 2003 that antihypertensive adherence ranged from 26-43% in developing countries, and that chronic poverty undermined remedial efforts.¹⁰ More recently, Médecins Sans Frontières reported that improving adherence to tuberculosis therapies would lower death rates and halt the emergence of extensively drug-resistant strains.¹¹ With the global burden of chronic health conditions, addressing adherence in lower-income settings has become a worldwide priority.¹⁰ The potential to simultaneously improve the quality of health care while also reducing costs is an elusive attribute of interventions and makes targeting nonadherence of great interest to all stakeholders in every health system.

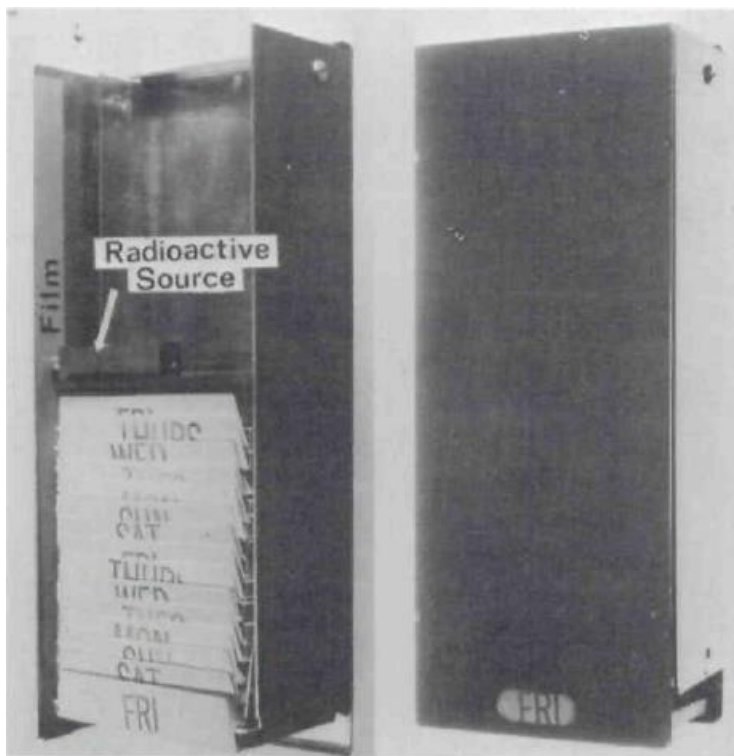
Addressing medication adherence has been recognized as a medical priority for quite some time. As early as 1947, Dr. Elliot Joslin and colleagues observed that the omission of routine outpatient insulin administration contributed to the admission of diabetic patients to the hospital.¹² In 1958, Dr. Wallace Fox cited Dr. Joslin's remark and stated that for tuberculosis:

“Although this [the comparative effectiveness between two anti-tuberculosis regimens at that time] is a very important issue it is less fundamental than the regularity with which patients will administer such medicaments to themselves for long periods of time. This is a major problem of long term chemotherapy in the treatment of any disease”.¹³

Dr. Fox argued that if doctors could find a way to identify these non-adherent patients, the problem could be addressed.¹³ In 1970, Dr. Thomas Moulding and colleagues cited Dr. Fox's work when they published their paper announcing a novel invention, the medication monitor.¹⁴

Their medication monitor used a radioactive source and photosensitive calendar to create a medication dispenser that could track each time the pill dispenser was opened as a surrogate measure of adherence.¹⁴ Dr. Moulding's medication monitor is depicted in **Image 1**. Dr. Moulding and colleagues reported that their medication monitor was able to identify "poor pill-takers" and should be used, "to study the factors that lead to irregular drug ingestion."¹⁴ They also demonstrated that their device could be used to reduce hospital expenses and recommended the routine use of their device for tuberculosis in particular.¹⁴

Image 1. Dr. Moulding and Colleagues' Medication Monitor



(Image originally published in: Moulding T et. al. Ann. Intern. Med. 1970; 73:559-564.)

Yet despite the subsequent years of research dedicated to improving medication adherence, even modern studies evaluating diverse interventions such as patient education, self-monitoring programs, family therapy, psychological therapy, telephone follow-up, and other supportive care measures have shown variable effectiveness.¹⁵ In fact, large prospective trials of motivational interviewing and eliminating copayments found only marginal improvements.^{16,17}

Additionally, the former interventions are resource-intensive, and the latter require well-integrated health care systems that may not exist in low-income settings.

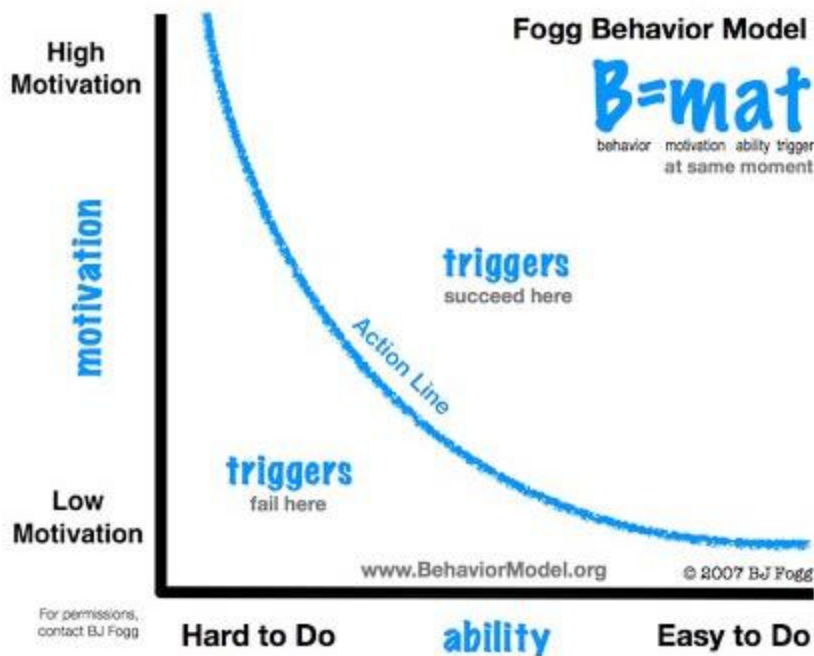
Addressing adherence through health information technology (HIT) is an alternate approach. Electronic pill monitors can now greet patients and remind them to take their medications, and provide alerts to physicians or other caregivers when preprogrammed drug-use schedules are missed.¹⁸ Such tools may help overcome troublesome aspects of other adherence interventions, such as unspecified content, variable delivery methods, and impracticality for clinical practice settings.¹⁹ As a result, HIT could promote efficient and low-cost improvements in adherence.²⁰ This class of devices, reminiscent of the kind described by Dr. Moulding and his colleagues, take advantage of modern technology rather than radioactive sources and photosensitive calendars to monitor adherence, and have added functionality including the ability to cue patient dosing events through various behavioral triggers including but not limited to audible beeps, flashing lights, information displayed on screens, and even wireless communication via text-messaging.

There is also theory available to help elucidate the way by which electronic pill monitors can modify adherence through their behavioral triggers. Dr. BJ Fogg, founder of the Persuasive Tech Lab at Stanford University, uses a model including motivation, ability, and triggers to explain how technologies can be used to influence human behavior. The model states that:

“Three elements must converge at the same moment for a behavior to occur: Motivation, Ability, and Trigger. When a behavior does not occur, at least one of those three elements is missing.”²¹

Applied to EMP, this model would suggest that patients will comply with medication regimens when they have sufficient motivation and ability to take their medications, provided they receive some form of a trigger to remind them to take their pills. While unique to each particular EMP device, these devices can be used directly to motivate patients, increase their ability, and provide triggers. Additionally, using an adherence record generated by an EMP device, health professionals including nurses, administrators, pharmacists, or doctors could use a patient’s adherence record as part of a separate intervention to influence motivation, ability, or triggers. Dr. Fogg’s own pictorial representation of his model of behavioral triggers is shown in **Figure 1**.

Figure 1. Fogg Behavior Model



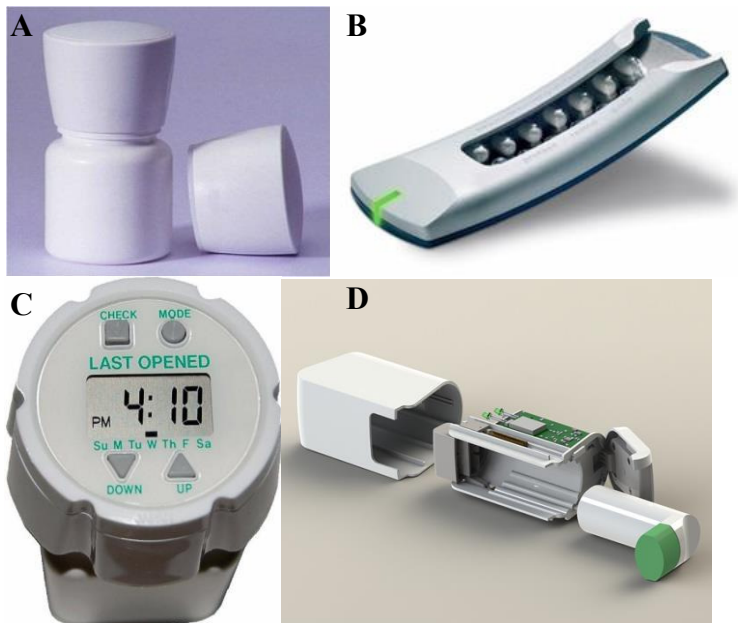
(Image found at <http://behaviormodel.org/> accessed on February 9th, 2015)

To study the application of one form of HIT to medication nonadherence, I conducted a systematic review of the effectiveness of electronic medication packaging (EMP) in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.²² EMP encompasses electronic devices integrated into the containers in which pills, inhalers, or other products. EMP is applicable in resource-poor settings because it requires little health care system infrastructure, although it can also be used as part of complex interventions. This systematic review examines the outcomes of EMP interventions, assessing the evidence about the efficacy of this approach, and identifying common features of successful EMP devices. Examples of EMP devices are shown in **Image 2**.

Discoveries related to increasing medication adherence are of great importance to researchers developing medication adherence devices, insurers seeking to maximize their investments in medications for improving health quality, pharmaceutical companies desiring to improve the effectiveness of their products, physicians seeking to improve the adherence of specific patients, and individual consumers considering purchasing these EMP products in the marketplace. The lessons are particularly relevant in low-income settings, where inexpensive EMP interventions may be a cost-effective intervention for policymakers seeking to improve

patient health outcomes. Even more broadly, medication adherence represents a rare case study in which an intervention can simultaneously improve the quality of health care while also reducing costs, examples of which are rare and are naturally of great interest to an even broader audience of stakeholders in health policy.

Image 2. Examples of Electronic Medication Packaging



A. Adherence Recording Only, Medication Event Monitoring System (Aardex) **B.** Audiovisual Reminder, Helping Hand Data Capture (Bang & Olufsen Medicom) **C.** Liquid Crystal Display, Prescript TimeCap (Wheaton Medical Technologies) **D.** Real Time Medication Monitoring (Evalan) (Images found at <http://www.klinische-pharmazie.info/forschung/bild-mems-dose/view>, <http://en.red-dot.org/2767.html>, <http://www.age-in-place.com/timecap.html>, and <http://welldesign.com/en/medical-product-development/health-evalan-%E2%80%93-adhaler-%E2%80%93-real-time-medication-monitoring/>, respectively, accessed on February 9th, 2015)

Methods

Data Sources

First, searches were conducted in the MEDLINE, EMBASE, International Pharmaceutical Abstracts (IPA), and PsycINFO databases using the OvidSP gateway, and in CINAHL and Sociological Abstracts via their respective interfaces, through October 1, 2013.

Literature reviews in related subject areas and the literature cited in known studies aided in formulating the search strategy and identifying a comprehensive list of search terms. In the OvidSP gateway, the following Boolean search was used: ((medication adherence or patient compliance).sh. or adheren*.ti,ab. or non-adheren*.ti,ab. or nonadheren*.ti,ab. or non-complian*.ti,ab. or noncomplian*.ti,ab.) and (prescription drug.sh. or drug*.ti. or medicat*.ti,ab. or pharmacother*.ti,ab. or pill*.ti,ab. or prescri*.ti,ab.) and ((technology.sh. or alarm*.ti,ab. or device*.ti,ab. or digital*.ti,ab. or electronic.ti,ab. or monitor*.ti,ab. or remind*.ti,ab. or remote.ti,ab. or technolog*.ti,ab.)). Similar searches were performed within the other databases. All searches were conducted in the English language. Search results were imported into a single grouping using EndNote X5, and screened for duplicate entries. A follow-up search on January 24, 2014 revealed no additional studies meeting entry criteria.

Study selection

Studies were included if: (1) they involved EMP, defined as electronic adherence-promoting devices integrated into the packaging of a prescription medication; (2) the medication at issue was a tablet, capsule, eye drop, topical cream, or inhaled agent prescribed on a routine ongoing schedule of administration; and (3) the authors reported results from a study testing the effect of the EMP on medication adherence. Studies acceptable for inclusion could have randomized, nonrandomized, controlled, prospective, or retrospective study designs. Case reports were excluded.

Although medication adherence is a key factor in health outcomes, studies that only reported health outcomes without accompanying adherence data were excluded because they could not make an uncontaminated link between their findings and adherence. The definition of EMP excluded other HIT adherence interventions, such as multi-pill dispensers and mobile phone-based interventions. Studies of medications prescribed on as-needed basis were also excluded. Studies of children or other patients whose adherence was mediated through another party were excluded.

To reach consensus on applying these criteria, two authors (KDC and ASK) reviewed a 10% sample of the search results independently and compared their results. One author (KDC) then screened the remaining abstracts and titles to identify studies for further review. Manual reference mining of studies and other reviews supplemented the search results.

Data extraction and analysis

Data were extracted (KDC) and checked (ASK), with disagreements resolved by consensus. Variables included: device name and major features; medication(s) studied; number of patients studied; study length; adherence outcomes; and supplemental findings including health outcomes, cost effectiveness results, and satisfaction surveys.

The studies were separated into relevant categories to facilitate evaluation. First, studies were divided into whether the EMP interfaced directly with the patient alone (“patient-interface only”) or was part of a broader intervention linked with a physician, pharmacist, or other caregiver (“integrated”). Within those two categories, the studies were qualitatively assessed to describe and evaluate the type of device: simple recorders; recorders with audio and or visual reminders; recorders with digital displays; recorders with audiovisual reminders and digital displays; or devices that used real-time wireless monitoring. Finally, for the integrated EMP interventions, the reported success of interventions that included patient feedback on adherence performance was compared with the results of interventions that did not provide feedback. Due to the heterogeneity of devices, interventions, medications, patient medical conditions, and settings, a formal meta-analysis was not possible.

Following data extraction, one author (KDC), unblinded to the results, assessed the studies for bias using the guidelines outlined in the Cochrane Handbook for Systematic Reviews of Interventions.²³ Studies were assessed for selection, detection, attrition, reporting, and other sources of bias. Selection bias was determined based on whether the method of sequence generation was a high-quality method such as random number generation, coin tossing, or minimization versus low-quality methods such as date of birth, or alternating order and whether the allocation order was adequately concealed from those recruiting participants. Detection bias was based on whether the participants and the personnel conducting the study were blinded to participants’ trial arm allocations. Attrition bias was determined by the magnitude of participants lost to follow-up, whether the dropout was even or uneven between trial arms, and whether any differences could be detected between those who completed the study and those lost to follow-up. Selective reporting was determined based on whether the study provided the expected measures of adherence based on the data available to the researchers, ideally but not necessarily based on a pre-registered trial protocol. We also included a domain that would

capture any additional sources of bias other than those already specified. Using this framework, overall bias would not just be the highest risk of bias in any domain. A study's overall risk of bias was determined based on the assessment of the aggregate of the biases and the potential of these sources of bias to affect the magnitude or direction of the results in accordance with the Cochrane Handbook.²³

Results

Search results and study sample

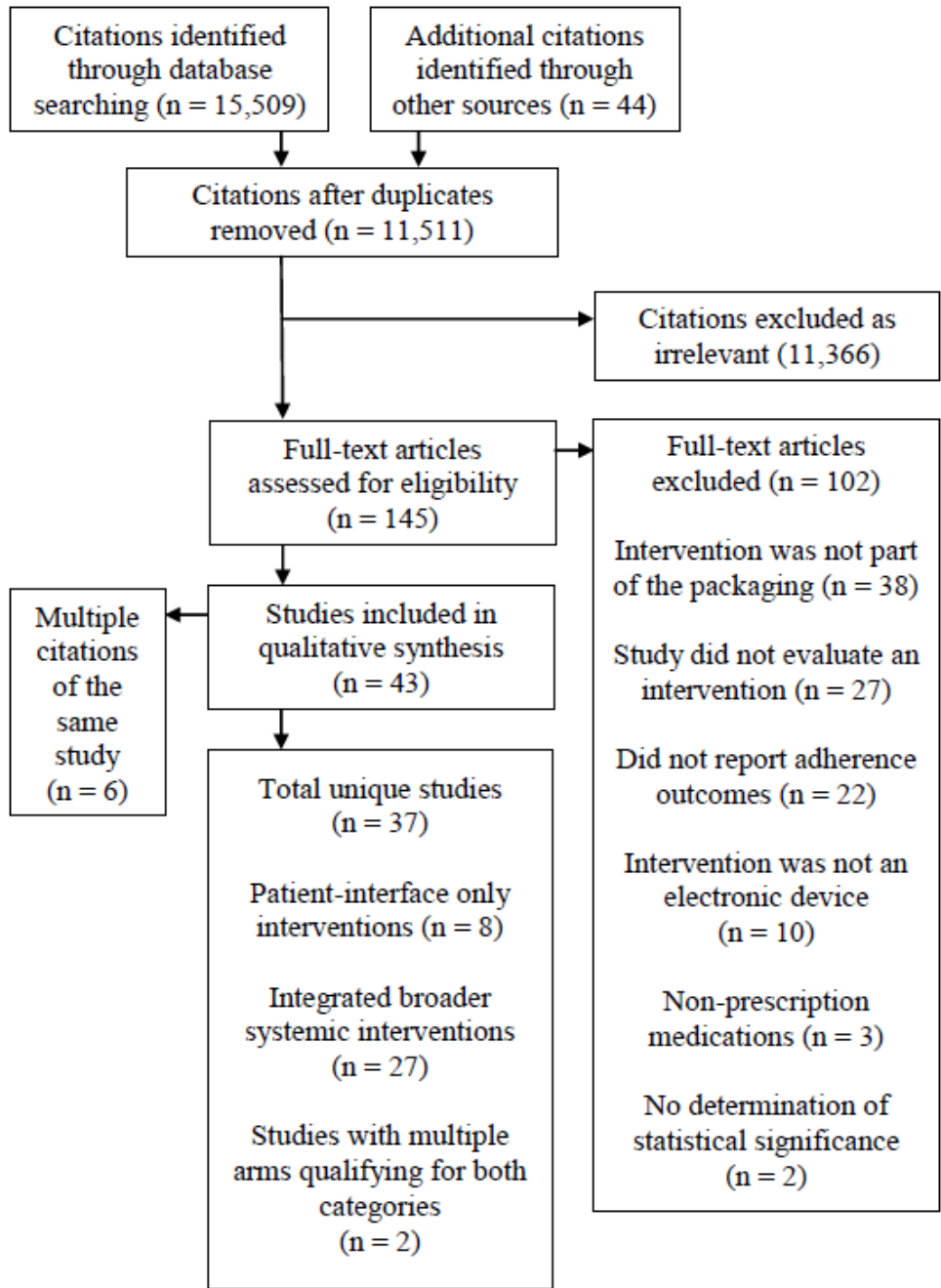
The search strategy identified 11,511 publications, of which 11,366 were deemed irrelevant after reviewing the titles and abstracts. Among the remaining 145 articles, 102 were excluded after full-text review because they did not meet intake criteria. The 43 remaining articles described 37 unique studies, of which 10 were patient-interface only and 29 were integrated into broader systemic interventions (**Figure 2**).²⁴⁻⁶⁶ Two of the studies contained multiple intervention arms that qualified for both categories.

The final sample of studies included experiences with 17 different devices and 14 different medical conditions: hypertension – 9; HIV – 6; psychiatric disorders – 4; diabetes/hyperglycemia – 3; glaucoma – 3; asthma – 2; heart failure – 2; smoking cessation – 2; chronic obstructive pulmonary disease – 1; hyperlipidemia – 1; hyperparathyroidism – 1; inflammatory bowel disease – 1; platelet inhibition – 1; and renal transplant – 1. The number of patients ranged from 5 to 1,523 (median 55, interquartile range [IQR]: 30-144), and the interventions lasted from 1 to 12 months (median 6, IQR: 3-9). There were 22 studies of simple recorders, 6 of recorders with audio and or visual reminders, 5 of recorders with digital displays, 5 of recorders with audiovisual reminders and digital display, and 1 study of a device using real-time wireless monitoring.

Effectiveness of EMP interventions

Overall, 56% (22/39) of the interventions reviewed found significant improvements in adherence attributable to EMP.

Figure 2. Study Flow Diagram



Patient-interface vs integrated interventions

Appendix 1 shows the studies of patient-interface-only devices. One-third (3/10, 30%) showed a significant effect on outcomes. One was a 6-month study of 90 patients with asthma using a device with audiovisual reminders. Charles et al. showed an inhaler that both beeped and

used an indicator light improved adherence to near-perfect level compared to controls using an inhaler without the reminders (93% vs 74%, $p < 0.01$).²⁸

A larger number of studies assessed integrated interventions (**Appendix 2**), of which about two-thirds showed significant improvement in adherence (20/29, 69%). The largest effect size was observed in a 6-month study of 15 hypertensive patients testing a device that combined adherence monitoring, a digital display and performance feedback. Compared with a control group of patients receiving usual care (27% adherence), there was a 73% increase in adherence in the intervention group ($p = 0.01$).^{64,65}

Two studies had multiple trial arms that enabled direct comparison of patient-interface-only and integrated interventions.^{27,30} In one study, the integrated intervention was more successful, and increasing the intensity of the interventions was associated with marginally higher improvements in adherence. McKenney et al. found higher adherence among hypertensive patients receiving medication containers with a digital display (94%), even higher for those receiving a digital display along with cards to record home and office blood pressure values (99%), and highest for those receiving the digital display, card, and a blood pressure cuff (100%, $p < 0.01$ for all three treatments compared to standard vials).³⁰ The other study by Kooy et al. found adherence was lower in a group with EMP and counseling as compared to EMP alone; however, adherence in both intervention arms was very high and the difference was not statistically significant (70.4% vs. 72.6%).²⁷

Performance of various EMP features

Certain characteristics of EMP produced improvements in adherence to varying extents. Five prominent characteristics of EMP interventions were identified: recording dosing events and storing a record of adherence, audiovisual reminders to cue dosing, digital displays, real-time monitoring, and providing patients with adherence performance feedback (**Table 1**).

Recorder and storage functions were included in every EMP device reviewed, making it the only ubiquitous feature of the EMPs studied. There were improvements in adherence in 64% (14/22) of the studies evaluating devices that only recorded and stored adherence records. While some devices recorded dosing events to provide accountability, the storage and export of adherence performance records also enabled complex interventions to be tailored to patient adherence patterns.

Digital displays were the next most common feature of EMP devices in the sample, and were subject to analysis in 10 studies. Information provided by the digital displays included: the time the bottle was previously opened; the amount of elapsed time since the last opening, and/or the number of times the container had been opened on that day.^{30-33,60-66} Five studies evaluated digital displays, showing effectiveness in 3. Another 5 studies tested devices that combined digital displays with audiovisual dosing cues; 4 improved adherence.

Table 1. Electronic medication packaging device features with positive effects on adherence

Device feature	Patient-interface-only EMP interventions (n positive studies/N total studies, %)	Integrated EMP interventions (n positive studies/N total studies, %)	Combined
Recorders only	0/2 (0)	14/20 (70)	14/22 (64)
Recorder+audio-visual reminder	1/4 (25)	1/2 (50)	2/6 (33)
Recorder+LCD	0/0 (0)	3/5 (60)	3/5 (60)
Recorder+audio-visual reminder+LCD	2/3 (67)	2/2 (100)	4/5 (80)
Real time (SMS)	0/1 (0)	0/0 (0)	0/1 (0)
Total	3/10 (30)	20/29 (69)	22/39 (56)

EMP=electronic medication packaging; LCD=liquid-crystal display; SMS=short message service

Audio or visual reminders to cue dosing were a less common feature of EMP devices in the sample, with 2 out of 6 (33%) showing effectiveness. The only device that utilized real-time monitoring did not show a significant improvement in adherence (0/1, 0%).

Most studies of complex interventions that provided opportunities for caregivers to give feedback to patients on their adherence patterns demonstrated improved adherence (18/24, 75%). Among the 15 studies that did not include such feedback, only 5 (33%) demonstrated improved adherence. For example, Rosen et al. found that patients using EMP linked to providers who were encouraged to give feedback and offer recommendations for remembering to take medications at specific times of day (“cue-dose training”) were more adherent than patients using the same EMP device without this feature of the intervention.⁶⁶

Thus, apart from the baseline monitoring and storing function present in all the devices, the features that most consistently had a positive effect on adherence were (1) combining digital displays that show the last time of container opening with audible reminder alarms and (2) providing patients with feedback on their adherence performance.

Secondary findings

Twenty-six studies (70%) reported supplementary data apart from the effect of the intervention on adherence. These fell into 5 non-mutually-exclusive categories: the impact of EMP on health outcomes (20 studies), subjective patient perceptions (4), factors other than EMP that affected adherence (4), the potential risks of EMP (1), and a cost effectiveness analysis (1).

Evidence of the impact of EMP on health outcomes was mixed. Ten of the 20 interventions (50%) found that EMP improved health-related outcomes; one found that the health of psychiatric patients using EMP worsened compared to controls.⁴³ However, only 14 of these 20 studies found significant improvements in adherence, and of those 14, 8 (57%) found that EMP improved the health of patients compared to controls. Unsurprisingly, EMP was more beneficial for health status when it increased adherence.

When patients were asked about EMP devices, most viewed their devices positively.^{31,56,57,63,66} Surveyed patients preferred smaller devices and the ability to disable device alarms when in public.⁶³ Additionally, all 3 (100%) of the studies that compared adherence on weekdays compared to weekends found that adherence was worse on weekends, and one of those studies also found evening doses were omitted more frequently than morning doses.^{53,60,61}

Two studies highlighted potential problems related to uptake of EMP. First, Wagner et. al. conducted a study using multiple measures of adherence and found that the self-reported adherence of patients using electronic caps declined in four weeks, which raised “concerns about the potential harmful effects of restricting the use of common adherence strategies such as pill organizers and ‘pocketing’ doses, which are requirements associated with electronic monitoring.”²⁵ Another concern emerged from studies investigating use of EMP for psychiatric drugs. One study found that psychiatric patients’ self-reported adherence to these drugs was actually lower than their electronic adherence record,⁵⁴ while another discovered that patients in the monitored group ended the study with higher levels of anxiety, depression, and somatic

complaints compared to the control group.⁴³ Both studies concluded that patients with psychiatric disease may have a difficult time adjusting to use of EMP.

Methodological quality and risk of bias assessments

A complete summary of the individual study methodological quality and risk of bias assessments is available in **Appendix 3**. The overall risk of bias for the included studies was moderate, with only 3 studies with a high risk of bias and 5 studies with an unclear risk of bias. Furthermore, only one of the 3 high-risk studies found a positive impact of EMP (Kruse et al.⁵³), while another of the high-risk studies (Wagner et al.²⁵) reported important potential problems with EMP. Simple patient-only interventions generally had lower risks of provider bias, which was more common in complex interventions that were characterized by providers delivering the active interventions. By electronically collecting the primary adherence outcome data, EMP naturally minimized the risk for assessor bias in most studies. Other sources of potential bias included using different measures of adherence for the intervention and control groups; however, this applied to only 3 studies. Overall, the minimal risk of bias found in the included studies did not suggest that this review would be subjected to undue bias favoring any particular conclusion.

Discussion

In this systematic review of studies evaluating the effectiveness of EMP, there is some evidence that both patient-interface-only and integrated interventions can promote medication adherence, with complex interventions commonly contributing to improved adherence. Providing patients with adherence feedback as a feature of interventions also led to improved rates of adherence. With respect to identifying successful characteristics of EMP devices, simple devices that monitor and store adherence records and devices that combine digital displays with audible reminder alarms appeared to be most useful at improving adherence.

The picture that emerges from this systematic review has implications for health systems, payers, providers, and patients considering use of EMP to address the pervasive problem of medication nonadherence. Even the most basic EMP enhanced medication adherence across multiple different drug classes and settings. In the best case, even simple recording and storage functions improved adherence by up to 38% when patients received feedback.⁴² Such

interventions could be straightforward to scale up, and may provide value particularly in settings around the world where hospital-based directly observed therapy programs are too expensive to implement.⁶⁷ Though there would be certain up-front costs—MEMS devices, for example, are estimated to cost \$25 per unit—this investment could potentially be compensated by the reduced health care costs in avoided hospital visits and complicated therapeutic interventions linked to poor adherence in common conditions including hypertension, HIV, and heart failure.^{4-6,68} Future studies investigating these opportunities would be of great value to patients and health systems alike.

While there is evidence to support implementing even limited EMP, the literature indicated that increasing the complexity and intensity of the EMP interventions further enhances their effectiveness in improving adherence. The importance of feedback to improving adherence is another consistent finding emerging from this review. Regardless of the type of device, interventions that generated feedback to patients were more successful than interventions that did not use the adherence records to provide feedback. Understanding the mechanism of the interaction between feedback and the performance of EMP interventions may help develop better approaches to improving adherence more generally.

Notably, however, not all studies reviewed found a positive effect between EMP and increased adherence. Several studies included control groups that received care beyond standard care, including scaled-down versions of the EMP interventions. Many studies reported unexpectedly high rates of adherence—in excess of 80%—in the comparison groups and at baseline, which far exceeds expected adherence rates in practice. This raises the possibility that intervention effects were masked by active effects in the control groups.

An unexpected secondary finding was that EMP can have an adverse impact in some settings, such as patients who use pill organizers and patients with psychiatric illnesses. It may be that EMP is most helpful when it augments an established organizational routine, or imposes a routine where one does not exist. In the limited circumstances in which EMP has paradoxical effects, it may interfere with an established physical or mental medication adherence habit. Those seeking to implement EMP should ensure they target patients who do not have effective medication adherence patterns already in place.

This study had certain limitations. First, numerous studies had methodological limitations such as nonrandomized designs, and many showed improvements that did not reach

the level of statistical significance. The risk of bias assessments indicates that the overall risk of bias was modest, and did not suggest that the analyses would be subjected to undue bias favoring any particular conclusion. This approach enabled us to collect a more complete picture of the experiences with EMP; however, the inclusive definitions of EMP and study designs also led to substantial heterogeneity in the results and ruled out the possibility of conducting a meta-analysis and forest plot. Publication bias is another important consideration since negative studies of EMP interventions may not have been submitted to journals for publications. In analyzing the results and drawing the conclusions, I relied to a greater extent on the larger prospective trials of EMP interventions which met conventional criteria of significance. In addition, most studies lasted less than 6 months. Longer-term evidence is needed regarding the use of EMP in patients with chronic illness, since the possibility exists that EMP, like other adherence interventions which have been studied, may lose its effect over time.¹⁵

This review was limited to English language articles and excluded studies of children; the global issue of medication adherence and the complex issue of medication adherence for children merit attention in subsequent analyses. Finally, this review focused on studies that measured adherence rather than only measuring health outcomes due to the potentially contaminated link between health outcomes and various intervention components in complex interventions where adherence was not measured separately. While secondary analyses indicated that studies that found improved adherence using EMP also had improved health outcomes, measuring the impact of EMP on health outcomes, and costs of care, should be a goal of future investigation.

Technological innovations in medication packaging have fundamentally changed the prospect of improving medication adherence, and solving the problem of medication offers a unique opportunity for every health system to improve patient health while also simultaneously reducing costs. This paper offers those pursuing EMP advice on how to maximize the effectiveness of EMP interventions. The literature summarized here suggests that health systems around the world considering EMP interventions will see the greatest improvements in outcomes from devices that utilize adherence monitoring and storage, digital displays combined with audiovisual alarms, and feedback to patients. EMPs that use these approaches represent promising tools to combat the intransigence of the medication non-adherence epidemic.

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Appendix 1. Characteristics and findings of studies testing patient-interface-only electronic medication packaging

Device name (manufacturer)	Medical condition	Total N	Trial length (mos)	Study details	Effect of device on adherence	Additional findings
ADHERENCE RECORDERS ONLY						
Medication Event Monitoring System (Aprex) ²⁴	Hypertension	1,523	3	RCT in a 1:2 design to compare Medication Event Monitoring System vs actively monitored pill counts (usual-care).	Good compliance (>80% of pills) observed in 92% of the Medication Event Monitoring System group vs 91% in usual care (p=ns).	
Medication Event Monitoring System (Aardex) ²⁵	HIV	173	1	RCT of three adherence surveillance methods: electronic monitoring caps, medication diaries, and a no surveillance control group.	Self-reported adherence 91%, 92%, and 94% for electronic monitoring caps, medication diaries, and controls, respectively (p=0.73).	
ADHERENCE RECORDER AND AUDIOVISUAL ALARM						
Helping Hand Data Capture (Bang & Olufsen Medicom) ²⁶	Hypertension	398	12	Crossover RCT comparing blister cards in a device with an auditory alarm or standard blister packs.	Compliance 45-52% in patients using alarmed blister packs vs 32-38% in patients using standard blister packs (p=ns).	The device did not affect BP control.
Compliance Card (Service Apotheek) ²⁷	Hyperlipidemia	182	12	RCT of electronic reminder device (ERD) delivered by mail vs usual care (control group).	Refill adherence was higher in the ERD group vs control group (72.6% vs 64.8%, p=0.18)	
Smartinhaler (Nexus6) ²⁸ *	Asthma	90	5.5	RCT of a metered dose inhaler with (intervention group) or without (control group) an audiovisual reminder function.	93% medication adherence in the intervention group vs 74% in control (18% difference, p<0.01).	
Travalert Dosing Aid (Alcon) ²⁹	Glaucoma	34	6	Observational study of patients who received an electronic monitoring device. In phase 1, the audible alarm was disabled and in phase 2 it was activated.	18% mean non-adherence in first period and 15% in second (p=0.06).	
ADHERENCE RECORDER, AUDIOVISUAL ALARM, AND LIQUID CRYSTAL DISPLAY						
Prescript TimeCap (Wheaton Medical Technologies) ³⁰ *	Hypertension	67	5.5	RCT of medication vial equipped with a cap that displays the last time the cap was removed vs a control group with standard medication vials.	Timepiece cap (without other compliance aids) associated with average compliance of 94% vs 79% in the control group (p<0.01).	Subjects using timepiece cap showed decrease in blood pressure (7.6 mm Hg systolic (p<0.01), 8.8 mm Hg diastolic (p<0.01)).

Intelligent Drug Administration System II (Bang & Olufsen Medicom) and Medication Event Monitoring System 6 SmartCap (Aardex) ³¹	Hypertension	24	4	Crossover RCT of blister packs showing the time since last opening and have an audible alarm (Intelligent Drug Administration System II) vs display the number of daily openings and hours since last opening (Medication Event Monitoring System 6 SmartCap).	At 2 months, 100% mean taking adherence for the Intelligent Drug Administration System II and 100% for the Medication Event Monitoring System 6 SmartCap (p=ns). Mean adherence for all participants at 4 months was 98.4%.	Patients considered both reliable reminders (Intelligent Drug Administration System II: 75%; Medication Event Monitoring System 6 SmartCap: 84%, p=ns).
Prescript TimeCap (Wheaton Medical Technologies) ³² *	Glaucoma	13	2	Crossover RCT of a cap that displays the last time the cap was removed vs standard caps.	Patient-reported adherence 96% with the device vs 83% without (p<0.01).	
ADHERENCE RECORDER AND REAL TIME MONITORING						
Real Time Medication Monitoring (Evalan) ^{33,34}	Diabetes / hyperglycemia	144	11	RCT of vials with Real Time Medication Monitoring (minus group), but without SMS or webpage access vs no intervention.	78% adherence for the minus group vs 72% for the control group (p=0.13).	

* Study achieved statistically significant improvement in adherence. N=number of participants, mos=months, ns=not significant, RCT=randomized control trial, HIV=human immunodeficiency virus, BP=blood pressure.

Appendix 2. Characteristics and findings of studies testing integrated electronic medication packaging interventions

Device name (manufacturer)	Adherence feedback (Y/N)	Medical condition	Total N	Trial length (mos)	Study details	Effect of the device on adherence	Additional findings
ADHERENCE RECORDERS ONLY							
Medication Event Monitoring System V TrackCap (Aardex) ³⁵	N	Hypertension	470	12	RCT of Medication Event Monitoring System and pill count (intervention group) vs pill count alone (control group) with adherence as outcome.	Adherence rates did not differ (96% vs 94%; p=0.97).	In both groups, systolic and diastolic blood pressure decreased similarly (23/13 vs 22/12 mm Hg in the intervention and control groups, p=ns).
Medication Event Monitoring System V (Aardex) ^{36,37 *}	Y	Heart failure	270	12	RCT of pharmacists' receiving monitoring data and delivering education to the patients vs usual care.	The intervention group had greater refill adherence than usual care (109% vs 105%, p<0.01).	Intervention saved \$2,960 per patient (CI \$7,603 to \$-1,338, p=ns) including the baseline intervention cost of \$205 per patient. The intervention group had 19% fewer exacerbations (incidence risk ratio=0.82).
Nebulizer Chronolog (Forefront Engineering) ^{38,39 *}	Y	Chronic obstructive pulmonary disease	205	4	RCT in which control group didn't know chronolog was recording actuations vs intervention in which participants informed of the device and given feedback.	Intervention group had greater percentage of sets with the prescribed number of actuations than control (81% vs 60%, p<0.01).	
Medication Event Monitoring System (Aardex) ^{40,41 *}	Y	HIV	116	9	RCT of minimal (for patients with >95% baseline adherence) and intensive intervention (for patients with <95% adherence) vs usual care.	Intervention improved timing adherence (mean difference = 7.40%, p<0.01).	The proportion of patients with undetectable viral load increased from 79% to 91% in the intervention group and decreased from 87% to 79% in the usual care group (p<0.05).
Medication Event Monitoring System 6 (Aardex) ^{42 *}	Y	Heart failure	82	9	RCT of education plus Medication Event Monitoring System feedback ("plus" group) vs theory-based education only ("light" group) vs usual care (control).	More patients in plus and light groups remained above the 88% cut point defining good adherence than controls (74%, 65%, and 36% for plus, light, and control groups; p=0.02).	Event-free survival longer for patients in intervention groups (p=0.01).

Medication Compliance Monitoring Device (US Patent Number 4,616,316) ⁴³	Y	Psychiatric disorders	67	4 to 8	RCT of feedback of monitoring device data and serum lithium levels vs serum lithium levels only.	Monitoring feedback had no effect on the proportion of patients with lithium levels in the appropriate range (68% intervention vs 65% control, p=ns).	Patients in the monitored group had higher adjusted scores for anxiety (p=0.03), symptoms of depression (p=0.02), and somatism (p=0.03).
Med-ic (Information Mediary Corp.) ⁴⁴ *	Y	HIV	64	12	RCT of electronically-monitored adherence feedback vs standard of care.	Mean adherence with intervention higher than controls (97% vs 85%, p<0.01).	The CD4 count rose by 90 cells/ μ l in intervention subjects vs a decline of 9 cells/ μ l among controls (p=0.02).
Medication Event Monitoring System (Aardex) ⁴⁵ *	Y	Smoking cessation	55	1.5	RCT of therapy with 10 min of Medication Event Monitoring System feedback vs therapy only.	Rates of dose compliance higher in intervention group (77% vs 54%, p<0.01).	Smoking abstinence rates did not differ between the two groups.
Medication Event Monitoring System (Aprex) ⁴⁶ *	Y	HIV	55	3	RCT of cue-dose training and feedback from Medication Event Monitoring System vs cue-dose training combined with cash reinforcement vs usual care.	Improvement in the cash reward group (p<0.01), but gains were followed by significant decreases by the time of follow-up (p=0.03).	No viral load change.
Medication Event Monitoring System (Aardex) ⁴⁷ *	Y	Platelet inhibition	48	6	RCT of providing feedback to patients using MEMS adherence data (Integrative Care, "IC") vs simply registering adherence using MEMs (Usual Care, "UC").	Adherence using the IC approach was higher than the UC strategy (99% vs 97%, p<0.01).	The difference in the vasodilator-stimulated phosphoprotein platelet reactivity index between the IC and UC strategies was not statistically significant (56.3 vs 43.7, p=0.7).
Medication Event Monitoring System IV (Aardex) ⁴⁸ *	Y	Smoking cessation	46	1.5	RCT of Medication Event Monitoring System with feedback showing adherence vs control patients not informed about Medication Event Monitoring System.	Compliance 73% in the feedback group vs 48% without (p<0.01).	
Medication Event Monitoring System (Aprex) ⁴⁹ *	Y	Psychiatric disorders	45	6	RCT of Medication Event Monitoring System vials with special instruction and reinforcing techniques vs Medication Event Monitoring System vials paired with usual care.	Compliance for the intervention group 76% vs 57% for the control group (p<0.01).	

Medication Event Monitoring System (unknown) ⁵⁰	N	Hypertension	35	4.5	Observational; participants had to remain hypertensive for two visits during an eight week observation period. These patients received an electronic medication monitoring device and instructions in its use as part of a 3 month intervention.	Compliance averaged 64% in the observational period and 83% in the intervention period (p=0.07).	Mean blood pressure in the cohort decreased from 171/101 mmHg to 153/90 mmHg over the entire study period (p<0.01).
Medication Event Monitoring System III (Aprex Corp.) ⁵¹	Y	Diabetes / hyperglycemia	32	2	RCT; Intervention providers received input from lab and Medication Event Monitoring System data, while the control providers received input based on lab data and pill counts alone.	There was no statistically significant difference in nonadherence rates when comparing pill count data in the control group (35%) with data in the MEMS group (60%, p=ns).	There was no significant change in the metabolic control of the subjects, 2 patients in each group improved to acceptable metabolic control (p=ns).
electronic Drug Exposure Monitor (Aardex) ⁵² *	Y	Psychiatric disorders	30	3	RCT of patients receiving special instruction from an electronic monitoring device at counseling sessions vs standard care.	Higher adherence in intervention group (88% vs 68%, p=0.03).	At the conclusion of the study, the mean Positive and Negative Syndrome Scale scores were 21 positive and 20 negative and 21 positive and 23 negative for the intervention and control groups, respectively (p=ns).
Medication Event Monitoring System (Aprex) ⁵³ *	Y	Hypertension	24	7 +/- 1	Observational; Compliance was measured in patients on antihypertensive therapy. Some patients received compliance feedback from their physician, others did not receive this feedback. It was at the doctors' discretion to use the compliance results for patient feedback or not.	Compliance higher in patients who received information vs those who did not (92% vs 82%, p<0.05).	Doses omitted more on weekends than weekdays 321/1388 vs 635/3479 (p<0.01). Evening doses omitted twice as often as morning doses 266/1711 vs 144/1711 (p<0.01).

Medication Event Monitoring System (Aardex) ⁵⁴	Y	Psychiatric disorders	22	3	Observational; Participants were recruited at inpatient psychiatric units and a community mental health center. Patients received feedback of their adherence performance, attentive listening, and teaching and management strategies. Clinicians delivered the intervention and monitored adherence weekly for the first month and at 2 and 3 months after enrollment in the study.	The intervention did not significantly increase adherence, which averaged 83% over the duration of the study (p=ns).	Self-reported adherence rates (75%) lower than electronic measurement (83%), which might be unique to psychotic population (p<0.01).
Metered-Dose Inhaler Chronolog, MC-311 (Medtrac Technologies) ⁵⁵ *	Y	Asthma	19	2.5	RCT of feedback on inhaled steroid use from the clinician investigator vs usual care.	Intervention adherence higher than control by week two (81% vs 47%, p<0.01). This treatment effect continued through week 10.	The FEV ₁ did not change significantly from baseline to week 10 in either group (+0.04 L and +0.16 L for the treatment and control groups, respectively, p=0.44).
Medication Event Monitoring System V TrackCap (Apres) ^{56,57} *	Y	Renal transplant	5	9	RCT of continuous self-improvement, consisting of individual data evaluation and system refinement in which personal system changes are identified and implemented training using Medication Event Monitoring System data, vs brochures.	Average adherence score for the continuous self-improvement group higher than the attention-control group's adherence score (p=0.03).	All (5/5) patients responded that participation in their respective intervention took "very little" or "just right" amount of time.
Medication Event Monitoring System (Aardex) ⁵⁸	Y	Inflammatory bowel disease	5	4	RCT of continuous self-improvement, consisting of individual data evaluation and system refinement in which personal system changes are identified and implemented using Medication Event Monitoring System data, vs educational information.	No change in the 3 month adherence score minus the baseline adherence score (p=0.14).	
ADHERENCE RECORDER AND AUDIOVISUAL ALARM							
Compliance Card (Service Apotheek) ²⁷	Y	Hyperlipidemia	245	12	RCT of electronic reminder device with counseling (Counseling with ERD) vs electronic reminder device delivered by mail (ERD) vs usual care (control group).	Refill adherence was lower in the Counseling with ERD group vs the ERD group (70.4% vs 72.6%, p=ns) and higher than in the control group (70.4% vs 64.8%, p=0.54)	

Dosing Aid (Alcon) ⁵⁹ *	N	Glaucoma	66	9	RCT of education, counseling, phone reminders, and an adherence device vs controls receiving usual care.	Mean adherence rate improvement was 19% (73% at follow up from 54% at baseline) for the intervention group vs 6% (51% from 46%) for controls (p=0.01).	No effect on intraocular pressure for the intervention group (p=0.96) or controls (p=0.34) comparing follow up and baseline values.
ADHERENCE RECORDER AND LIQUID CRYSTAL DISPLAY							
Medication Event Monitoring System 6 SmartCap (Aardex) ⁶⁰	Y	HIV	145	12	RCT of patient feedback using graphical readouts by clinical staff vs patients blinded to feedback and not given graphical output.	Medication execution was high in both groups (>90%), but feedback was not associated with a significant difference (p=ns).	Execution worse over weekends (p<0.01).
Medication Event Monitoring System (Aardex) ⁶¹	N	Hypertension	62	3	RCT; After 4 weeks of run-in, normotensive patients were placed in one comparison group (A) and the remaining still uncontrolled patients were randomized to receive either a simple Medication Event Monitoring System and self-BP measurement intervention (B) or a teaching program and interactive Medication Event Monitoring System intervention (C). All groups were then followed for 8 weeks.	There was no statically significant difference between the randomized groups (B vs C) in either days with correct intake or the percentage of prescribed number of doses taken (p=ns).	In both intervention groups, significant reductions of systolic blood pressure were observed (162 mmHg vs 148 mmHg for group B and 161 mmHg vs 142 mmHg for group C; p < 0.025). Compliance on the weekends vs weekdays was 50% (confidence interval=28.1–90.0).
Medication Event Monitoring System SmartCap (Aardex) ⁶² *	Y	Hyper-parathyroidism	41	6	RCT of providing feedback to patients using MEMs adherence data at 2 month intervals (Integrative Care, "IC") vs simply registering adherence using MEMs (Usual Care, "UC").	Comparing mean adherence at months 2 and 6, adherence increased by 10.3% in the IC group and decreased by 5.5% in the UC group (p=0.02).	The median change in intact parathyroid values was better in the IC group than in the UC group (-94 ng/L vs +113 ng/L, p<0.01).
Medication Event Monitoring System 6 SmartCap (Aardex) ⁶³ *	Y	HIV	19	3	Observational; Adherence was measured with Medication Event Monitoring System caps for 2 months before the intervention and 3 months during the intervention. Adherence data were used to provide feedback to participants during the nurse-led intervention.	Mean adherence (percentage of prescribed doses taken within correct time interval) before the intervention was 82% compared to 93% during the third month of the intervention. (p<0.05).	Patients scored the content of the program at 8.2 on a scale of 1–10. Some patients complained about MEMS user friendliness, container size, and shape, causing 3 participants to not complete the whole intervention period.

Medication Event Monitoring System SmartCap (Aprex) ^{64,65} *	Y	Hypertension	15	6	RCT of feedback, counseling, education, an instruction card, and an electronic cap with a digital display vs usual care.	At the end of the intervention, the treatment group had median adherence of 100% vs 27% for control (p=0.01).	Systolic blood pressure improved in the intervention group at week 12 (median 130 vs 152 mm Hg, p<0.01). Diastolic blood pressure unchanged.
ADHERENCE RECORDER, AUDIOVISUAL ALARM, AND LIQUID CRYSTAL DISPLAY							
Prescript TimeCap (Wheaton Medical Technologies) ³⁰ *	N	Hypertension	67	5.5	RCT of vial with a cap that displays the last time the cap was removed vs vials with a display cap and cards to record home and office BP values vs standard medication vials (control).	99% compliance for device and card vs 100% compliance for device, card, and a blood pressure cuff vs 79% in controls (p<0.01 vs each intervention group).	The cap and the card decreased blood pressure (1 mm Hg systolic and 7.6 mm Hg diastolic, p<0.01 vs controls). Cap, card, and cuff decreased blood pressure 15 mm Hg systolic and 6.6 mm Hg diastolic (p<0.01 vs controls).
Medication Event Monitoring System SmartCap (Aardex) ⁶⁶ *	Y	Diabetes / hyperglycemia	33	7.5	RCT of caps that display hours since last opening, cue-dose training, and adherence feedback vs display caps without training or feedback.	Adherence was approximately 60% prior to randomization increased to 80% in the cue-dose training group by week 16 vs around 60% in controls (p=0.02).	Mean helpfulness rating of MEMS feedback review on Likert scale of 1-5: patients = 3.9, providers = 3.4. Mean uncomfortableness ratings for feedback review is 1.0 for both patients and providers.

* Study achieved statistically significant improvement in adherence. Y/N, yes/no, N=number of participants, mos=months, ns=not significant, RCT=randomized control trial, HIV=human immunodeficiency virus, CI=confidence interval, MEMS=medication event monitoring system, FEV1=forced expiratory volume in 1 second.

Appendix 3. Methodological quality and risk of bias assessment summary

Citation	Study	Design	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (detection)	Blinding of outcomes assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other	Overall
²⁴	Barrios, 2007	RCT	Unclear	Unclear	High	Unclear	Low	Low	High	High
²⁵	Wagner, 2002	RCT	Unclear	Unclear	High	Unclear	Low	Low	High	High
²⁶	Christensen, 2010	Crossover RCT	Unclear	Unclear	Unclear	Low	Low	Low	Low	Low
²⁷	Kooy, 2013	RCT	Low	High	High	Low	Unclear	Low	Low	Low
²⁸	Charles, 2007	RCT	Low	Low	Low	Low	Low	Low	Low	Low
²⁹	Hollo, 2008	Observational	N/A	N/A	Low	Low	Low	Low	Low	Low
³⁰	McKenney, 1992	RCT	Unclear	Unclear	Low	Unclear	Low	Low	Low	Low
³¹	Santschi, 2007	Crossover RCT	Low	Unclear	High	Low	Low	Low	Low	Low
³²	Laster, 1996	Crossover RCT	Unclear	Unclear	Low	Low	Low	Low	Low	Low
^{33,34}	Vervloet, 2010 & 2011	RCT	Low	Low	Unclear	Low	Low	Low	Low	Low
³⁵	van Onzenoort, 2011	RCT	Unclear	Unclear	Low	Low	Low	Low	Low	Low
^{36,37}	Murray, 2004 & 2007	RCT & CEA	Low	Low	High	Low	Low	Low	Low	Low
^{38,39}	Tashkin, 1991& Nides, 1993	RCT	High	High	High	Low	Low	Low	Low	Low
^{40,41}	De Bruin, 2010 a & b	RCT	Unclear	High	High	Low	Low	Low	Low	Low

42	Wu, 2012	RCT	Unclear	Unclear	High	Low	Low	Low	Low	Low
43	Elixhauser, 1990	RCT	High	High	High	Low	Low	Low	Low	Low
44	Sabin, 2010	RCT	Low	High	High	Low	Low	Low	Low	Low
45	Mooney, 2007	RCT	Unclear	Unclear	High	Low	Unclear	Low	Low	Unclear
46	Rigsby, 2000	RCT	Low	Low	High	Low	Low	Low	Low	Low
47	Forni Oгна, 2012	RCT	Unclear	Unclear	High	Low	Unclear	Low	Low	Unclear
48	Schmitz, 2005	RCT	Unclear	Unclear	High	Low	Unclear	Low	Low	Unclear
49	Cramer, 1999	RCT	Unclear	Unclear	High	Low	Low	Low	Low	Low
50	Waeber, 1999	Observational	N/A	N/A	High	Unclear	Low	Low	Low	Unclear
51	Matsuyama, 1993	RCT	Unclear	Unclear	Low	Low	Low	Low	High	Low
52	Kozuki, 2006	RCT	Unclear	Unclear	High	Low	Low	Low	Low	Low
53	Kruse, 1994	Observational	N/A	N/A	High	Low	Low	Low	Low	High
54	Kozuki, 2005	Observational	N/A	N/A	High	Low	Low	Low	Low	Low
55	Onyirimba, 2003	RCT	Unclear	Unclear	High	Low	Low	Low	Low	Low
56,57	Russell, 2010 & 2011	RCT	Unclear	Unclear	High	Low	Low	Low	Low	Low
58	Matteson, 2011	RCT	Low	Low	High	Low	Low	Low	Low	Low
59	Okeke, 2009	RCT	Low	Low	High	Low	Low	Low	Low	Low
60	Davies, 2010	RCT	Unclear	Unclear	Unclear	Low	Low	Low	Low	Low
61	Mengden, 2006	RCT	Unclear	Unclear	High	Low	Low	Low	Low	Low
62	Forni Oгна, 2013	RCT	Low	Unclear	High	Low	Low	Low	Low	Low
63	De Bruin, 2005	Observational	N/A	N/A	High	Low	Low	Low	Low	Low
64,65	Ruppar, 2010 a & b	RCT	Low	Low	High	Low	Low	Low	Low	Low
66	Rosen, 2004	RCT	Unclear	Unclear	High	Low	Unclear	Low	Low	Unclear

Other=risk of bias from sources other than those specified in other columns; Overall=overall risk of bias; RCT=Randomized controlled trial; N/A=not applicable; Low=low risk of bias; Unclear=unclear risk of bias; High=high risk of bias