ABSTRACT

Background: Many patients experience difficulties adhering to medication regimes. For people who forget or get confused about medication, there are products to help them such as multi-compartment medication devices (MMDs). Some of these, known as electronic MMDs (eMMDs), use audible and/or visual signals to prompt the patient when to take medication, dispense medications, give instructions to the patient, and contact a caregiver (mobile internet or text to a carer) as needed.

Aim: To systematically review the literature on the use of eMMDs, to determine what evidence for their effectiveness is available.

Methods: A comprehensive literature search of 10 databases, plus an internet search and hand searching was conducted, using the MeSH terms reminder systems/patient compliance/medication adherence. There were no date restrictions. Inclusion criteria were patients in any community setting, in any country and with no restrictions of age, gender, ethnicity or medical condition, using an eMMD. Peer-reviewed quantitative or qualitative studies of any design were included.

Results: Of 805 abstracts identified and 99 full text papers retrieved, six met the inclusion criteria. Five of the studies reported adherence to medication regimes; one reported design factors to improve adherence. Adherence varied by the context of the reminders, the target group and usability of the devices. The studies were small scale and only one was a well conducted randomised controlled trial.

Conclusion: Overall methodological quality of the studies was poor. Although positive effects on adherence were reported further, rigorously conducted, studies are needed to inform the use of eMMDs.

Keywords: Medication device, patient adherence, reminder systems.

INTRODUCTION

15 million UK adults[1] are living with chronic disease, 30% of whom have multiple morbidity requiring polypharmacy, and many have some level of cognitive impairment. This number is estimated to double by 2030[2]. Medication adherence problems are common and associated with poor disease control including hospitalisation and death[3-8]. There are also other financial implications; it has been estimated that in the UK the cost of medications unused and returned to pharmacists[9] is £100 million per annum.

Non-adherence may be unintentional or intentional. Unintentional non-adherence is usually due to practical problems such as poor instructions, poor memory or cognitive defects~~, multiple medications to be taken~~ or difficulty in opening packaging[10]. Intentional non-adherence is largely associated with poor motivation and negative beliefs about medication. While both types of non-adherence can result in failure to take any of the medicine, the most common form of non-adherence is doses missing because of forgetfulness, changed medication schedules or busy lifestyles[11~~0~~].

A review[12~~1~~] of medication adherence identified four general categories to improve adherence: patient education; improved dosing schedules; increased access to health care; and improved communication between physicians and patients. Strategies to improve dosing schedules were described, including the use of pillboxes to organize daily doses, simplifying the regimen to daily dosing, and cues to remind patients to take medications. Another review[13~~2~~] which assessed current research on determinants of patient adherence found that multifaceted interventions are most likely to improve adherence. A recent Cochrane review[14~~3~~] of interventions to improve adherence found that while almost all of the effective interventions were complex these did not lead to large improvements in adherence and treatment outcomes.

A Kings Fund report on polypharmacy[15~~4~~] noted that adherence problems increase as medicine regimens become more complex. It concluded that there is a need to develop systems that optimise medicines use for patients taking multiple medications, to

Formatted: Superscript

maximise benefit, minimise risk and reduce harm and waste. Solutions proposed included training programmes, improved electronic decision support for clinicians and/or patients, patient-friendly information systems, the use of monitored dose systems and clinical audit. A report on the use of multi-compartment compliance aids[165] (MCAs) concluded that MCAs may be of value for some patients who have been assessed as having practical problems in managing their medicines. The ease of use of MCAs has also been investigated[176] as problems with accessing medication from its packaging in a MCA had been reported by 54% of participants. This suggests that modifications need to be made and it may be that electronic storage and dispensing methods with reminder systems could be a useful addition if they are found to increase adherence.

There are now electronic Medicine Management Devices (eMMDs) that can prompt the patient when to take a medicine using audible and/or visual signals, dispense medicines at the appropriate times, give instructions to the patient, and contact a caregiver (usually by mobile technology) if medicines are not removed or are not taken at the right time. Reminders and alerts can be set up by health care professionals or carers. Such devices are heavily promoted by manufacturers and described in government policy documents[187]. However, it is not known if these electronic devices provide any advantage over regular MMDs in terms of better adherence to a medication plan.
The aim of this systematic literature review was to determine: if there is evidence that the use of eMMDs improves adherence; for which patient groups and for which condition types they are most likely to be successful in improving adherence and health outcomes; how acceptable are they to users, carers and health care professionals and if there is evidence of cost savings from their usage.

METHODS

Inclusion criteria

Studies were included from all community settings and countries and no restrictions were made in terms of patients' age, gender, ethnicity, medical condition or types of

medication. Peer-reviewed qualitative and quantitative studies of all designs were included.

Studies investigating multi-compartmental devices which met at least one of the following criteria were included:

1. Prompted the patient when to take a medicine using audible and/or visual signals and/or dispensed medicines at the appropriate times.
2. Gave instructions to the patient, and/or contacted a caregiver if medicines were not removed or were taken at the wrong time.

Outcomes

Outcomes to be collected included adherence measures, clinical outcomes, usability, and satisfaction with the intervention.

Search methods for identification of studies

The MeSH terms for the database search were reminder systems/ patient compliance/ medication adherence. See Appendix 1 for detailed search terms.

The databases of the Cochrane Central Register of Controlled Trials (Trials along with EED and HTA) and the Database of Abstracts of Reviews of Effects (DARE), MEDLINE, EMBASE, CINAHL, EBSCO, PsycINFO, Scopus, ASSIA and Web of Science were searched. Current Controlled Trials was searched to identify trials in progress. The Internet was searched using the Google academic search engine (http://scholar.google.com) looking at the first 300 returns on the relevance ranking, electronic reminder system manufacturers contacted, and abstracts from the Pharm-line database checked. Internet search terms were based on the MeSH terms for drug administration and drug delivery systems and reminder systems along with the specific trade names. Reference lists of papers retrieved in full text for relevant studies were also searched. Hand searches of journals and meetings abstracts were carried out. There were no language restrictions

applied in the initial search, however full text versions of papers not published in English were excluded as no translation service was available. There were no date restrictions.

Selection of studies

The search strategy (see Appendix 1) was implemented by MP on 26 March 2014 and references imported to Endnote and duplicates removed. MP checked all the titles and abstracts of potentially relevant studies and these were independently checked by at least one other member of the research team. Full text copies of potentially relevant studies were obtained and these were assessed by MP and one other member of the team for their eligibility for inclusion against the criteria outlined above. Disagreements were resolved by discussion.

Data extraction and management

The following data were extracted by two independent reviewers (MP and one other member of the team) from the studies using a customised data extraction form in Excel:

- Country and setting
- Study design
- Participants (sample size, mean age, gender ratio)
- Medical condition/medication
- eMMD system
- Adherence measure
- Other reported outcomes including clinical outcomes, acceptability, barriers and facilitators to the use of eMMDs, the experience and usability of the devices
- Study tools e.g. questionnaire
- Costings

Quality assessment and reporting biases in included studies

Studies were assessed for the risk of potential bias using the Critical Appraisal Skills Programme (CASP)[198] questions as appropriate to the study design. For randomised

controlled trials (RCT) this included allocation procedures, blinding, attrition, power of study and whether positive results had been stressed over negative results. For a cohort study this included: the population, subjective or objective measures, accuracy of outcome measurement to minimise bias, and consideration of confounding factors if they were identified. For a qualitative study this included the rigour of data collection, the type of analysis and clarity of the statement of findings. Using the answers to the questions as an indication of quality, an overall quality assessment for each study was determined.

Summary measures and synthesis of results

Where available, the difference in mean adherence was reported. Otherwise the studies are reported narratively.

RESULTS

Study selection

A total of 805 titles/abstracts was identified. After removal of duplicates 749 abstracts were screened, of which 650 were excluded as they contained no explicit mention of electronic reminders. Full text articles were obtained for the remaining 99. Three articles, identified from citation lists or the grey literature were rejected because they had not been peer reviewed. The PRISMA chart is shown in Figure 1.

Study characteristics

Six articles met the full inclusion criteria and the main characteristics are summarised in Table 1. The studies were conducted between 2008 and 2013, in countries in North America, Europe and Asia. There was a range of study designs from observational studies (3), a controlled longitudinal study (1) and RCTs (2). The studies used eMMDs with different levels of sophistication of electronic reminders but all with alarms that were triggered by different contextual factors or with the facility to contact users or carers. Hayakawa et al.[2019] interviewed 116 patients attending (as outpatients)

cardiovascular or metabolic disease departments to inform the development of an eMMD, followed by a feasibility study in which 10 patients used the device. Hayes et al.[210] used adherence to vitamin pills to explore the effectiveness of a complex reminder intervention in 10 elderly people where forgetfulness was an issue. Lo et al.[221] carried out an ethnographic study observing the use of an eMMD followed by a satisfaction survey of 30 healthy volunteers to explore the desired properties and the barriers to use of such a device. Schmidt et al.[232] conducted a controlled longitudinal study of 62 patients with high blood pressure and congestive heart failure (CHF) taking antihypertensive medication to determine if an eMMD could improve adherence. Simoni et al.[243] used an eMMD combined with cognitive behavioural therapy (CBT) in a RCT with 40 HIV positive patients with depression taking anti-retroviral medication. Stip et al.[254] tested an eMMD in a RCT of 47 people with schizophrenia taking anti-psychotic medications.

Effects of the intervention on adherence rates

Hayakawa et al. tested the design and feasibility of a smartphone based reminder system which linked wirelessly to a pillbox and included real-time medication monitoring. According to the self-reports from 116 interviews 46 (41.1%) patients forgot to take their medication, or took their medication more than two hours behind schedule, more than once a week. In the feasibility study of the pillbox with 10 patients, delay in taking medicine within the scheduled time occurred 47 times out of 127 (37.0%) and in 17 of the 47 occasions (36.2%) patients took their medication upon being presented with only one reminder.

Hayes et al. compared three types of reminder systems in older patients who lived alone and were considered to be poorly adherent. They reported that adherence rates varied with the situation in which prompts were administered. Context-aware prompting which only occurred when participants had forgotten to take their pills and were in a situation where they were likely to be able to take their pills, resulted in a mean adherence of

92.3% (95% CI 84.7-97.0). Using time based reminders alone adherence was 73.5% (95% CI 68.0-78.6), and with no prompting 68.1% (95% CI 57.5-80.5). Adherence was tracked by the eMMD.

Schmidt et al. studied adherence when using an eMMD in patients with CHF taking antihypertensive medication who had self-reported or physician reported compliance problems (n=32). Medication intake data was transferred by the eMMD to an electronic health record and was monitored by health care professionals. Compliance was measured by the number of interventions needed to remind patients to take medication if they failed to take medication when the alarm went off. More than 50% of patients made only 0-2 mistakes during the 2 month period although this varied greatly with one patient needing 19 interventions.

Simoni et al. conducted a RCT to examine the efficacy of a CBT intervention for depression used simultaneously with an eMMD (Medsignals®), compared to an identical pillbox with the alert system deactivated and with no CBT, in patients with HIV receiving antiretroviral therapy who were sub-optimally adherent. Adherence was monitored by self-reports using a visual analogue scale[26~~5~~] and an embedded log in the pillbox that recorded compartment openings and uploaded the data to a web based system. They reported that greater adherence was recorded by the intervention group using the eMMD with an odds ratio of 3.78 (SE=1.31, 95% CI=1.62-7.26, p=0.001). Similar findings were reported for the self-reports (OR=3.34, SE=1.31, 95% CI=1.62-7.26, p=0.001).

Stip et al. conducted a RCT to test if an eMMD (DoPill®) with an alarm and real time information improved adherence in schizophrenic patients taking anti-psychotic medications compared with a control group using a Medication Events Monitoring System (MEMS®) device which only recorded openings. The use of the eMMD showed a mean antipsychotic adherence rate (AAR) (number of pills taken / number of pills prescribed X 100) of 67% which was comparable for both devices. The raw results indicated that

more adherent patients at baseline evidenced greater improvement in adherence relative to more non-adherent patients, with ARRs of 98-100% when using the eMMD. This suggests there may be a limit to the benefit that electronic aids can have for increasing adherence in those who are not simply forgetful. Adherence was also measured by the Brief Adherence Rating Scale (BARS) ratio, a self-report and clinician assessment of adherence which is used to assess medication adherence in schizophrenia and was reported in the literature[276] to show an AAR of about 49.5% in the general schizophrenic population. The AAR measured by BARS in this study was found to be 86-99% suggesting that BARS was not an accurate indicator of adherence in this group of participants.

Effects of the intervention on health outcomes

Simoni et al. reported improved biological markers of cell counts for HIV viral load for patients taking antiretroviral drugs and psychological indicators of depressive symptoms using the Beck Depressive Inventory-1A (BDI-IA) and the Montgomery-Åsberg Depression Rating Scale (MADRS). The primary depressive symptoms outcomes were assessed with a self-report on the BDI-IA and a semi-structured interview by an independent rater blind to treatment condition using the MADRS. Intervention participants demonstrated a greater drop in depressive scores in BDI-IA scores (OR = -3.64, SE=1.78, 95% CI=-7.26 to 0.01, p = 0.05) and to a lesser extent MADRS scores (OR=-5.14, p=0.14). Biological markers indicated some relative improvement for CD4 cell count (OR = 69.45, SE = 38.57, 95 % CI = -6.16 to 145.05, p = 0.07), but not for viral load (OR=0.14, 95%CI=-0.75-1.03, p=0.75).

Schmidt et al. compared the intervention group with a control group of CHF patients (n=30) who did not have adherence problems, did not use the eMMD and had better mental and physical health at baseline. They found a significant improvement in mental health in the intervention group based on self-reported health status in the 12-Item Short Form Health Survey[27] (T= -3.09, p≤0.01) from baseline to the 2 month

assessment. The mental health of the control group did not change significantly (T=1.81, p=0.05) in this time.

Usability issues

Lo et al. found an eMMD could enhance adherence if it could be used flexibly in different contexts, was not too large, the alarm was not so intrusive that it overcame privacy if used outside the home and interface complexity was reduced to simplify the operating system. Older adults in the feasibility study of 30 patients (15 > 65 years, 15 < 65 years) preferred a pillbox that integrated both pillbox and reminder functions rather than using a separate mobile phone as the reminder. Hayakawa et al. found 51 out of 112 (45.5%) took their medications outside the home more than once a week, suggesting that portable pillboxes may support medication self-management. Schmidt et al. found the features with the most potential for improvement were more flexible programme timing and mobile solutions for the pillbox. Hayes et al. identified benefits for the elderly in not being required to carry medication dispensers but rather having a system that monitors their movements to determine when medication prompting should be carried out.

Limitations of the studies

All the studies included in the review had methodological problems. They were limited by small numbers, inadequate control groups and often included complex interventions of which adherence technology was only a part. The limitations are summarised in Table 2. The CASP quality assessment tools were used to determine the quality but due to the mixed methods used by the studies a full comparison was not meaningful. A cost analysis was not reported in any of the included studies.

DISCUSSION

This review suggests eMMDs may improve adherence. However all the studies had methodological limitations, and larger, well conducted controlled trials, with longer term

outcomes are required to confirm this. SStudies using anof eMMDs as use the technology as both the intervention and the tool to measure adherence, the intervention cannot separate the adherence measurement tool which may introduces bias. making it difficult to assess the sole effect of the eMMD which may also partly explain the low effect found. Most Furthermore most of the studies in this review were at the feasibility stage and did not report in detail on clinical outcomes. The elderly with cognitive problems and patients with conditions where timing and adherence to medication regimes are critical were the groups most likely to benefit from these more sophisticated reminder devices. The usability, mobility of the device and the flexibility of timing of reminders were identified as issues that still need to be addressed.

Previous reviews in this area have focused on electronic reminders but not particularly on eMMDs. A review by Fenerty [2928] found no significant difference in adherence rate for patient reported results compared to electronic monitoring systems. It was unclear whether one type of reminder system had a significant impact on adherence. The review concluded that the type of medication could influence the adherence rate and that chronic and asymptomatic illnesses may be most resistant to adherence-enhancing strategies. Similarly Vervolet [3029] reviewed studies using electronic reminders but only one of the papers in this review concerned an eMMD and this was included in our review. The review provided evidence for the short term effectiveness of electronic reminders but the effects in the long term were unclear.

This review showed that electronic reminders combined with MMDs may have the potential to lead to improvements in patients' adherence to medication but the context, usability and medical condition influence their usefulness. Further high quality studies in a range of contexts are required to establish if the use of eMMDs as a long term aid or possibly as an interim tool to achieve adherence is effective and cost-effective.

Review team

Brian McKinstry, Christine Bond, Moira Kinnear and Mary Paterson

Competing Financial Interest

None in relation to this study

Funding

The study was supported by the Chief Scientist Office [grant number CZH/4/968].

References

(1) Long-term conditions compendium of Information: 3rd edition. *Department of Health* 2012.

(2) Prince, M, et al. World Alzheimer Report 2013: Journey of Caring: An analysis of long-term care for dementia [Online] 2013; http://www.alz.co.uk/research/WorldAlzheimerReport 2013.pdf (accessed 12 April 2014)

(3) Burke L et al. Compliance with cardiovascular disease prevention strategies: a review of the research. *Annals of Behavioral Medicine* 1997; 19: 239-63.

(4) Cresswell K, et al. Adverse drug events in the elderly. *British Medical Bulletin* 2007; 83: 259-74.

(5) Leendertse, et al for the HARM study. Frequency of and risk factors for preventable medication-related hospital admissions in the Netherlands. *Arch Intern Medicine* 2008; 168(17): 1890-96.

(6) Budnitz D et al. National surveillance of emergency department visits for outpatient adverse drug events. *JAMA* 2006; 296: 1858-66.

(7) Committee on Quality of Health Care in America IoM. Crossing the quality chasm: Washington DC. *National Academies Press* 2001.

(8) Smith J. Building a Safer NHS for Patients: improving medication safety. London. *Department of Health* 2004.

(9) Prescribing costs in primary care. *National Audit Office* 2007.

(10) Horne R et al. Concordance, adherence and compliance in medicine taking, *Report for the National Co-ordinating Centre for NHS Service Delivery and Organisation R & D (NCCSDO)* 2005.

(10) Stone, VE. Strategies for optimizing adherence to highly active antiretroviral therapy: lessons from research and clinical practice. *Clin Infect Dis* 2001; 33: 865-72.

(11) Osterberg L, Blaschke T. Adherence to medication. *The New England Journal of Medicine* 2005; 353: 487-497.

(12) Kardas P et al. Determinants of patient adherence: a review of systematic reviews. *Frontiers in Pharmacology* 2013; 4: 91.

(13) Nieuwlaat R et al. Interventions for enhancing medication adherence. *Cochrane Database of Systematic Reviews* [Online]. 2014; Available: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD000011.pub4/abstract.

(14) Durenden et al. Polypharmacy and medicines optimisation. *The Kings Fund* 2013.

(15) Improving patient outcomes: The better use of multi-compartment compliance aids. *The Royal Pharmaceutical Society* 2013.

(16) Adams R. et al. Do older patients find multi-compartment medication devices easy to use and which are the easiest? *Age and Ageing* 2013; 42: 715-720.

(17) eHealth Strategy 2011-2017 *Scottish government* [Online] 2011; http://www.scotland.gov.uk/Publications/2011/09/09103110/9 (Accessed 23 March 2014)

(18) *Critical Appraisal Skills Programme (CASP) 2014. CASP Checklists Oxford.* [Online] 2014; Available: http://www.casp-uk.net/ (Accessed 15 March 2014)

(2019) Hayakawa M et al. A Smartphone-based Medication Self-management System with Real-time Medication Monitoring. *Applied Clinical Informatics* 2013; 4: 37-52.

(21) Hayes T L et al. A study of medication-taking and unobtrusive, intelligent reminding. *Telemedicine and e-Health* 2009; 15: 770-776.

(22) Lo Y L et al. Electronic Medication Reminder for Older Adults. In: Kurosu, M, ed. *Human Centered Design,* 2011.

(232) Schmidt S et al. Acceptance of telemonitoring to enhance medication compliance patients with chronic heart failure. *Telemedicine and e-Health,* 2008; 14: 426-433.

(243) Simoni J M et al. A preliminary RCT of CBT-AD for adherence and depression among HIV-positive Latinos on the U.S.-Mexico border: The Nuevo Dia study. *AIDS and Behavior* 2013; 17: 2816-2829.

(254) Stip E et al. A randomized controlled trial with a canadian electronic pill dispenser used to measure and improve medication adherence in patients with schizophrenia. *Frontiers in Pharmacology,* 2013; 4 AUG.

(265) Amico K R et al. Visual analog scale of ART adherence: association with 3-day self-report and adherence barriers. *J Acquir Immune Defic Syndr.* 2006; 42(4): 455–9.

(276) Byerly M J et al. The Brief Adherence Rating Scale (BARS) validated against electronic monitoring in assessing the antipsychotic medication adherence of outpatients with schizophrenia and schizoaffective disorder. *Schizophrenia Research* 2008; 100: 60-69.

(287) Ware JE et al. A 12-Item Short Form Health Survey (SF-12): Construction of scales and preliminary tests of reliability and validity. *Med Care* 1996; 32: 220–233.

(298) Fenerty S D et al. The effect of reminder systems on patients' adherence to treatment. *Patient Preference and Adherence* 2012; 6: 127-135.

(3029) Vervloet M. The effectiveness of interventions using electronic reminders to adherence to chronic medication: a systematic review. *J Am Med Inform Assoc*. 2012; 19: 696-704.