Medication Adherence: Emerging Use of Technology

Bradi B. Granger[1] and **Hayden Bosworth**[2]

[1]Duke Translational Nursing Institute, Duke University School of Nursing, Duke Heart Center and Duke University Health System, Durham, North Carolina

[2]Center for Health Services Research in Primary Care, Durham VAMC and Department of Medicine, Division of General Internal Medicine; Department of Psychiatry and Behavioral Sciences, School of Nursing, Duke University

Abstract

Purpose of Review—Adherence to proven, effective medications remains low, resulting in high rates of clinical complications, hospital readmissions and death. The use of technology to identify patients at risk and to target interventions for poor adherence has increased. This review focuses on research that tests these emerging technologies and evaluates the effect of technology-based adherence interventions on cardiovascular outcomes.

Recent Findings—Recent studies have evaluated technology-based interventions to improve medication adherence by using pharmaceutical databases, tailoring educational information to individual patient needs, delivering technology-driven reminders to patients and providers, and integrating in-person interventions with electronic alerts. Cellular phone reminders and in-home electronic technology used to communicate reminder messages have shown mixed results. Only one study has shown improvement in both adherence and clinical outcome. Current trials suggest that increasing automated reminders will compliment but not replace the benefits seen with in-person communication for medication-taking.

Summary—Integration of in-person contacts with technology-driven medication adherence reminders, electronic medication reconciliation and pharmaceutical databases may improve medication adherence and have a positive effect on cardiovascular clinical outcomes. Opportunities for providers to monitor the quality of care based on new adherence research are evolving and may be useful as standards for quality improvement emerge.

Introduction

Adherence is defined as the extent to which a person's behavior corresponds to desirable healthcare goals jointly established with the healthcare provider [1, 2]. In cardiovascular disease, adherence to medications is low – over 50% of patients do not take medications as prescribed [3, 4]. The rate of poor adherence has remained stable over two decades [5]: 40% of patients fail to fill an original prescription [6, 7], and over 50% discontinue medications within a year [8-14].

The relationship between adherence to medications and clinical outcomes has been clearly demonstrated [15, 16, 17], particularly in cardiovascular disease. Serious complications, increased hospitalization, and death are associated with poor pill refill and no-fill rates for post-procedural antiplatelet drugs [18], as well as medications for chronic use in hypertension [19], hyperlipidemia [20] and heart failure [21]. Non-adherence to antiplatelet

Correspondence to: Bradi B. Granger, RN, PhD 8020 Willardville Station Rd. Bahama, NC 27503 grang004@mc.duke.edu W (919) 684-1622 Fax (919) 479-0953.

medication (clopidogrel) following intracoronary stent placement, resulted in higher rates of readmission, repeat procedures, and a three-fold greater likelihood of death [12, 22, 23]. Poor medication adherence following myocardial infarction was associated with higher rates of readmission and 30-day mortality [24], while better adherence to evidence-based medications for heart failure mediated event-free survival [25].

Despite the benefits of taking evidence-based medicines as prescribed, poor adherence is a major global public health challenge [1]. Research on its theoretical underpinnings [26], barriers and facilitators [27, 28], and devices and interventions to improve adherence [29-31] serve to illuminate the complexities of medication adherence and difficulties with achievement on a population level. Practical ways to improve adherence, particularly in chronic illness, eludes patients and healthcare providers. Effective interventions are labor intensive [32-34], cost prohibitive [35, 36], and ineffective long-term [13, 14, 30], among a majority of chronic illness patients needing life-long strategies to maintain medication-taking [37]. Most cardiovascular illnesses are accompanied by co-morbid conditions, requiring complex multiple-medication regimens [38, 39], increasing the likelihood of poor adherence [38, 40-42].

New studies are evaluating emerging technology-based approaches to improve medication adherence [43-48]. This paper synthesizes these studies and identifies key lessons learned for clinical practice settings and strategies for integrating quality performance measures for adherence.

Emerging Technologies To Improve Medication Adherence

Existing evidence-based adherence interventions are plagued by high resource intensity, lack of specificity regarding content and delivery, and impracticality for everyday clinical practice settings [33]. Recent trials addressed these issues by testing defined, technology-enhanced interventions with replicable, clearly described components aimed at generalizability and sustainability [49-52]. Despite advances in clarity, replicability, and study design, interventions to improve adherence have produced mixed results. Clinical trials of technology-based interventions can be broadly categorized into two groups: automated detection and reminder systems [42, 53, 54] and in-person systems with an electronic component [20, 52, 55-58] (Table 1). The following section describes differences in intervention components, adherence rates, and clinical outcomes among recent trials of adherence systems.

Pharmaceutical database technologies and automated alerts

Pharmaceutical database technology identifies patient-level adherence patterns for filling newly prescribed medications and refills, providing a community-based point of contact with patients beyond the time constraints of hospital or clinic visits. Pharmacists are accessible and convenient for most patients and family caregivers, are knowledgeable information sources, and are able to identify and discuss potential contraindications or concerns regarding active medications. Pharmacy-generated data allows identification and analysis of the proportion of days that patients *have access to* medication, as either a medication possession ratio (MPR) or cumulative medication gaps (CMG) metric [59]. Besides these metrics, electronic data systems can be programmed to generate phone call reminders to patients regarding the need for pill refill.

A study of hypertensive patients (n=398) using automated reminders in conjunction with electronic monitoring devices showed no significant benefit in either medication adherence or blood pressure control compared to standard therapy controls (Christensen and colleagues [54]). Similarly, in a study by Gazmararian and colleagues [42] using automated reminders

alone, patients did not interact consistently with the available technology [42]. In this primarily indigent, inner city population (N=275) using automated pharmaceutical database triggers, telephone reminder calls, and picture cards to address low health literacy, researchers found no significant change in refill adherence in the intervention or control groups. Adherence rates for medication dosing and timing in the intervention versus control groups were 45 and 52%, respectively, in the first 6 months, and 32 and 38% in the second 6 months after randomized groups were crossed-over.

Electronic pharmaceutical data systems have also been studied regarding physician use. Tamblyn and colleagues [58] showed these systems can be programmed to alert physicians to the need for medication reconciliation and are effective in improving the frequency of medication reconciliation by providers. In their study (n=2293 patients), a significant increase in drug profile review occurred in the intervention group compared to controls (44.5% versus 35.5%, respectively), but without significant medication changes (therapeutic optimization of medications) by physicians or improved rates of refill adherence by patients.

Although electronic reminders on pagers, cell phones and text-messages have been studied, randomized clinical trials conducted in 2010 to test interventions based on these technologies suggest that electronic automated triggers alone are ineffective for improving pill refill adherence. Nor do they produce meaningful change in physician actions related to medication reconciliation.

Telemonitoring systems for medication-related self-management

In contrast to pharmacy-generated reminder systems, in-home telemonitoring systems allow patients to generate and respond to their own data. Patients or caregivers record and report symptoms, such as shortness of breath or weight gain, and associated medication dosing, which can be reviewed by the provider for evaluation of trends. Home telemonitoring systems, pioneered by Cleland and colleagues [60], automatically monitor blood pressure, blood glucose, and daily weight changes, among others. In addition, telemonitoring systems offer opportunities for medication-related education, reinforcement, and opportunities for review and reconciliation. Uses of a bi-directional communication strategy supports patient-provider communication and accessibility..

The risk is user error. Patients must choose (and be adequately skilled) to 'connect' to the electronic system, and providers must choose (and be adequately available) to respond. New systems obviate the need for conscious provider response by automatically 'sending' the information to a central server and generating an alert for values outside of normal range, which is then automatically sent to the provider's cell phone or computer screen.

In recent randomized trials of new-generation telemonitoring systems, results have been disappointing. In the most recent trial [53], heart failure patients (n=1653) were randomized to telemonitoring (n=826) versus usual care (n=827). Telemonitored patients received symptom education and assessment and reported medications and daily weights from home. Alert values and patient concerns were transmitted electronically to the central server for nurse follow-up within 2-3 days. At the conclusion of the study there was no significant difference between the intervention and control groups in all-cause or heart failure-related hospital readmissions or death. Patients also reported no difference in symptom recognition or medication use. Thus, telemonitoring alone appears to be ineffective in improving outcomes related to medication use and clinical outcomes of self-management in patients with heart failure [61-63].

Combination In-Person and Electronic Technology Interventions

Combinations of in-person *with* automated reminders or triggers has produced the most effective results for improving medication adherence and clinical outcomes, as well as patient and caregiver satisfaction with information, accuracy of the active medication list, and improvements in patient-provider partnership or person-centeredness of care. The most successful large-scale adherence intervention, the COM99 study, randomized physician practices (n=79) to a 3-part in-person intervention for patients with uncontrolled hypertension [52]. Providers conducted pill counts, designated a family member to support medication adherence behaviors at home, and provided educational information to patients and families. Patient participants (n=877) were more adherent (O.R. 1.91, 95% confidence interval 1.19 to 3.05) and had better controlled blood pressure (O.R. 0.62, 95% confidence interval 0.50-0.78) compared to the control group at 6 months.

Similarly, in a study by Robinson and colleagues [57], personal communication with patients by community-based pharmacists about blood pressure monitoring, hypertensive medication management, and adherence behaviors significantly improved adherence (0.91% vs. 0.78%, p=0.02) and reduced systolic blood pressure (by 9.9mmHg in intervention group versus 2.8 mmHg in controls, p<.05) at 6 months; 12 month outcomes showed no significant difference, demonstrating lack of sustainability of the effects. Eussen and colleagues [20] also showed that in-person communications by community pharmacists (n= 26 pharmacies randomized; n=899 intervention subjects, n=460 control) effectively improved medication adherence to statin therapy at 6 months but was not sustained to 12 months.

By contrast, a multidisciplinary implementation study by Bosworth and colleagues among Medicaid patients (N=588) with uncontrolled hypertension and poor adherence (55% baseline MPR) showed improved medication adherence for 12 months [55]. Using a pre-post observational cohort design, the study evaluated MPR 12 months prior to implementing an in-person telephone intervention by care managers to a stable cohort of patients prescribed at least one anti-hypertensive agent. Following implementation, the MPR was 77% and was sustained at 12-months post-implementation.

Resource Intensity and impracticality of administering interventions in a single clinical setting

The interventions described above are labor intensive, time-consuming, and expensive. Follow-up phone calls, frequent patient contact, and unlimited provider access are financially burdensome for the healthcare system. Although investigators have demonstrated the cost-effectiveness of such interventions [64, 65], many community hospitals and physician practice groups find the cost prohibitive [66, 67].

Interventions are also difficult to sustain for patients with chronic illness. Many interventions have failed to show long-term effectiveness, in part because of unproven community-based follow-up and reinforcement in a sustainable, system-wide delivery format [68]. Self-care interventions for late-stage chronic illness are particularly problematic in terms of standardization since patients who do not feel well are increasingly and unavoidably dependent on others to facilitate care, including medication-taking [37].

Moving Toward Adherence-Dependent Quality and Performance Measures

Consistent with current emphases on quality, access, and equity of care [69], the cardiovascular literature emphasizes performance measures in which medication adherence contributes to quality score cards, affecting not only mortality but also more intermediate treatment targets: blood pressure and lipid control and decreased symptom-associated readmissions [70-74]. The link between medication adherence and treatment targets is

robust;, although practical approaches that help patients improve medication adherence are lacking. For this reason, the World Health Organization has distinguished between modifiable and non-modifiable risk determinants [2]. In a clinical setting, nonmodifiable factors might serve as 'flags' to alert providers to communicate especially carefully with patients, whereas modifiable factors might serve to trigger specific patient-problem interventions.

Adherence to medications is increasingly recognized as requiring shared goal setting between patients and providers [75]. Tailored, telephone-scripted nursing interventions have shown success in improving medication adherence, alleviating the time commitment of the primary care provider and lowering system and provider costs [50, 76]. However, these programs have not been tested in real-world settings and are only now being implemented in large, prospective, population-based cohorts [55].

Implications for Provider-Based Performance Measures

Quality of care is evaluated using performance measures established by the Centers for Medicare and Medicaid Services (CMS)[72], derived from evidence-based practice guidelines, such as the American Heart Association and American College of Cardiology guidelines for care [77], and supported by national healthcare policy and quality groups such as National Quality Forum [78]. Performance measures include providing optimal evidence-based treatments at the correct dose and time and providing adequate information to patients at discharge to the home setting. Patient and provider indicators of medication adherence are tied to these performance measures and are publicly reported at patient, provider, and healthcare system levels [79-81].

Provider compliance with clinical guidelines has differed by treatment. For example, compliance with ACE-I in heart failure was 80-90%, but beta-blocker use was far less optimal, ranging from 27% in usual care groups to 55%-67% in intervention groups [82, 83]. Provider performance in achieving evidence-based guideline targets has improved [84], and interventions that improve provider compliance improve clinical patient outcomes [85], including decreased hospital readmission rates and hospitalized days.

New recommendations for improvement of provider compliance with guidelines include use of checklists and information technology upgrades to enable electronic documentation systems to provide guideline-based prompts [86, 87]. A similar approach may help providers in ambulatory and community clinic settings, and may also improve 'self-care' for patients and family caregivers in the home.

Implications for Patient-Centered Performance Measures

Treatment targets for selected cardiovascular patients include blood pressure, blood glucose levels (HgA1C), smoking status, and daily weight fluctuations. Providers' ability to influence these targets is based on patients' ability to adhere to evidence-based, prescribed medications. Thus, provider interventions are under increasing scrutiny to include adherence interventions, and performance scores are increasingly dependent on physicians' ability to affect medication-taking, even for patients with long-term chronic illness.

One approach to integrating adherence interventions into standard patient care is to assess medication-taking behaviors during each initial patient assessment [70]. A short series of questions can help to assess patients' medication-taking behaviors and plan effective communication and intervention [88].

New multidisciplinary and home-based interventions to improve CMS measures of patient outcomes, cost, and efficiency of care include early recognition of poor adherence,

decreased rates of complications, and prevention of hospital readmission [34, 50]. Strategies to facilitate adherence have included using reminders, reinforcements, rewards, and feedback on patient progress; providing education; reinforcing cognitive cues through use of question/answer sessions; improving process variables, such as waiting time, transportation to center or clinic, and the convenience of parking; improving system variables, such as carefully evaluating the frequency of scheduled follow-up; and improving the availability of and access to healthcare providers. Although these interventions have improved monitoring of early signs and symptoms and decreased hospitalizations and mortality, mortality remains an impractical performance measure for most cardiovascular diseases, particularly at the local clinical level. While early heart failure management and home-based nursing intervention programs showed improved mortality [89-91], in recent trials, their effect on mortality was not significant [92, 93].

More practical measures focus on Institute of Medicine quality indicators other than mortality, such as patient satisfaction with information given and the safety, quality and efficiency of care transitions from one setting to another [68, 94, 95]. Transitions between settings (Figure 1) offer opportunities for improving medication adherence when health systems integrate dedicated personnel and time for medication reconciliation, communication of prescription changes, tele-home monitoring and in-person follow-up calls. Such strategies implemented over time and *across* settings and episodes of care help patients meet treatment targets more effectively [34, 94, 96, 97]. They go beyond single-setting applications or automated telephone reminders to intervene at each episode of chronic care, using technology to maintain continuous communication between providers, monitor and track prescriptions and refills, decrease early discontinuation of beneficial medications, and improve adherence. These new interventions also include pharmaceutical cost-sharing programs and incentive-based insurance programs.

Conclusion

Although many variables are associated with adherence, few are consistently strong predictors, and a predictive profile of poor adherence has not been established. Nevertheless, recent findings regarding adherence to cardiovascular medications show a consistent relationship between medication adherence and clinical outcomes, and therefore have implications for quality-based performance measures that target clinical outcomes. Starting with a simple checklist and an assessment of adherence on first clinical contact, and integrating technology-based reminders with in-person communication may help both patients and providers to get started [86].

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Key points

1. Poor adherence to medications is associated with higher rates of clinical complications, re-hospitalizations and death in cardiovascular disease.

2. New interventions to improve adherence use emerging technology, such as automated electronic alerts and reminders for refill of prescriptions.

3. Passive delivery or use of technology-based interventions alone, without an active, in-person component, are not effective in improving adherence rates or patient outcomes.

4. Feasible clinical strategies to improve adherence include routine assessment of patient adherence and use of in-person interventions to reinforce and support technology-based triggers.
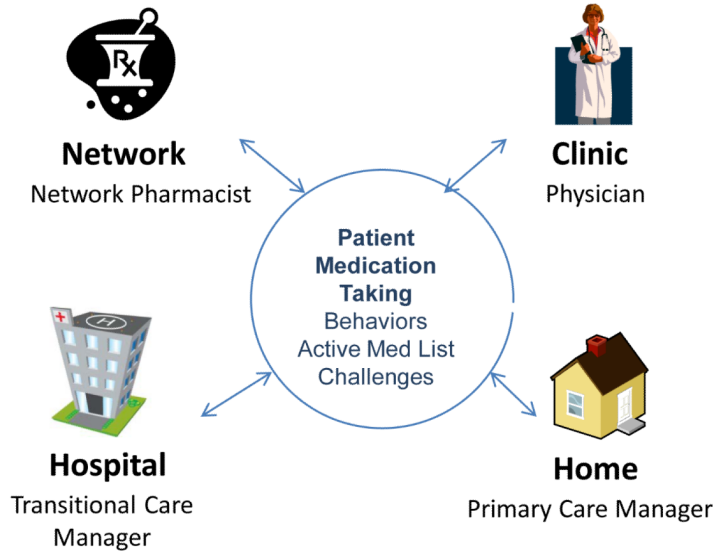
Figure 1.
Example of Pharm Assist intervention: a multiple-step pathway representing key components of behavior reinforcement for medication adherence. Modified from the Community Care of North Carolina Pharmacy Home Project. Troy Trygstad, PharmD, PhD

Table 1

Summary of Randomized Clinical Trials and Implementation Research for Medication Adherence Interventions

Author	Design	Patients	Intervention	Aims / Outcomes	Results
Bosworth, 2011 [55]	Multicenter, nonrandomized pre-post implementation evaluation	n=558, Medicaid patients prescribed at least one HTN drug	Tailored, telephone intervention Delivered by care managers	Medication adherence – as measured by medication possession ratio (MPR)	Medication adherence (medication possession ratio) improved from 55% 9-12 months prior to the intervention to 77% 9-12 months after implementation. Sustainability (12 months) of the intervention demonstrated.
Chaudhry, 2010 [53]	Multicenter, randomized controlled trial	n=1653 patients with HF and recent HF hospitalization	Randomized to: Group 1: telemonitoring (n=826) Group 2: usual care (n=827)	Primary: All cause readmission or death within 180 days after enrollment Secondary: HF hospitalization; length of stay; hospitalization frequency	No difference in primary endpoint No difference in secondary end points or any of its components.
Christensen, 2010 [54]	Multicenter, randomized controlled trial with treatment - control group cross-over at 6 months	n=398 patients on telmisartan once daily	Randomized to: Group 1: electronic compliance monitoring with a reminder and monitoring device Group 2: standard therapy Groups crossed over after 6 months.	Medication adherence – as measured by medication electronic monitoring device Blood pressure control.	No difference in BP 6% improved medication adherence in intervention group at 6 months 2% improved medication adherence in intervention group at 12 months.
Eussen, 2010 [20]	Multicenter, randomized controlled trial	n=899 subjects on statin therapy Group 1: n=439 pharmaceutical care Group 2: n=460 usual care	• 5 counseling sessions by pharmacist • Structured education about medication adherence • Lipid levels measured • Association between adherence and lipid levels discussed	Medication adherence – as measured by drug discontinuation	Lower discontinuation rate at 6 months in intervention versus usual care (HR 0.66, 95% CI 0.46 to 0.96). No difference between groups at 12 months (HR 0.84, 95% CI 0.65 to 1.10). Median MPR was very high (>99%) in both groups and did not differ between groups.
Gazmararian, 2010 [42]	Multicenter, prospective, nonrandomized controlled trial	N=275 Group 1: (n=173) intervention group Group 2: (n=102) control group Primarily indigent, minority population	3-part intervention: a. automated telephone reminder calls to refill prescriptions,	Medication adherence – pill refill as measured by cumulative medication gap (CMG)	No difference in change in medication adherence before and after intervention between intervention and control groups (p = 0.4)

Author	Design	Patients	Intervention	Aims / Outcomes	Results
			b. picture prescription card for health literacy **c.** clear health communication training for pharmacists		
Pladevall, 2010 [52]	Multi-center, clusterrandomized controlled trial	(n=79) Physician practices (n=877) Patients	Practices randomized to: Group 1: counted patients' pills, designated a family member to support adherence behavior, and provided educational information Group 2: usual care	Primary: blood pressure control at 6 months. Secondary: medication adherence and a composite end point of all-cause mortality and cardiovascularrelated hospitalizations	Improved blood pressure (odds ratio 0.62, 95% confidence interval 0.50 to 0.78) at 6 months. Improved adherence (odds ratio 1.91, 95% confidence interval 1.19 to 3.05) at 6 months. After 5 years, 16% of the patients in the intervention group and 19% in the control group met the composite end point (hazard ratio 0.97, 95% confidence interval 0.67 to 1.39).
Powell, 2010 [56]	Multiple-hospital, partially blinded behavioral efficacy randomized controlled trial	n=902 HF patients	Randomized to: Group 1: Education • 18 telephone contacts • heart failure education tip sheets (mailed) • 1 year Group 2: Self-Management • tip sheets in group sessions • taught self-management skills to implement the tip sheet advice.	Primary: death or HF hospitalization	No difference in the education vs. self-management group (163 [40.1%)] vs 171 [41.2%], respectively; odds ratio, 0.95 [95% confidence interval, 0.72-1.26]). No differences on any secondary end points, including death, heart failure hospitalization, all-cause hospitalization, or quality of life.
Robinson, 2010 [57]	Quasi-experimental study (matched intervention and control pharmacies)	n=18 chain community pharmacies n=180 patients in pharmaceutical care n=196 patients in usual care	Group 1: Pharmaceutical care groups: Educational training of pharmacists in hypertension therapies, monitoring, and management Group 2: Usual care groups; no pharmacist training	Medication adherence	Improved BP: average reduction in systolic BP was 9.9 mm Hg in PC patients compared with 2.8 mm Hg in UC patients (p < 0.05). Based on patient self-report, PC patients were more likely to say that they take their medicines as prescribed compared with UC

Author	Design	Patients	Intervention	Aims / Outcomes	Results
					patients (p < 0.05). Adherence rate was higher in PC patients (0.91 +/− 0.15) compared to UC patients (0.78 +/− 0.30) (p = 0.02) at 6 months No significant difference in adherence rate at 7- to 12-months
Tamblyn, 2010 [58]	Multicenter, randomized controlled trial	n=2293 primary care patients prescribed lipid-lowering or antihypertensive drugs	Randomized to: Group 1: adherence tracking and alert system Group 2: active medication list alone	Drug profile review, changes in cardiovascular drug treatment, and refill adherence in the first 6 months	Significant increase in drug profile review in the intervention compared to the control group (44.5% v. 35.5%; P < 0.001), No significant increase in drug discontinuations due to side effects (2.3% v. 2.0%; P = 0.61); and a reduction in therapy increases (28.5% v. 29.1%; P = 0.86). There was no significant change in refill adherence after 6 months of follow-up.