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International Series: Adherence

# Adherence: a review of education, research, practice, and policy in the United States

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**ABSTRACT***

Objective: To describe the education, research, practice, and policy related to pharmacist interventions to improve medication adherence in community settings in the United States.

Methods: Authors used MEDLINE and International Pharmaceutical Abstracts (since 1990) to identify community and ambulatory pharmacy intervention studies which aimed to improve medication adherence. The authors also searched the primary literature using Ovid to identify studies related to the pharmacy teaching of medication adherence. The bibliographies of relevant studies were reviewed in order to identify additional literature. We searched the tables of content of three US pharmacy education journals and reviewed the American Association of Colleges of Pharmacy website for materials on teaching adherence principles. Policies related to medication adherence were identified based on what was commonly known to the authors from professional experience, attendance at professional meetings, and pharmacy journals.

Results: Research and Practice: 29 studies were identified: 18 randomized controlled trials; 3 prospective cohort studies; 2 retrospective cohort studies; 5 case-controlled studies; and one other study. There was considerable variability in types of interventions and use of adherence measures. Many of the interventions were completed by pharmacists with advanced clinical backgrounds and not typical of pharmacists in community settings. The positive intervention effects had either decreased or not been sustained after interventions were removed. Although not formally assessed, in general, the average community pharmacy did not routinely assess and/or intervene on medication adherence.

Education: National pharmacy education groups support the need for pharmacists to learn and use adherence-related skills. Educational efforts involving adherence have focused on students' awareness of adherence barriers and communication skills needed to engage patients in behavioral change.

Policy: Several changes in pharmacy practice and national legislation have provided pharmacists opportunities to intervene and monitor medication adherence. Some of these changes have involved the use of technologies and provision of specialized services to improve adherence.

Conclusions: Researchers and practitioners need to evaluate feasible and sustainable models for pharmacists in community settings to consistently and efficiently help patients better use their medications and improve their health outcomes.

**Keywords:** Medication Adherence. Pharmacists. Education, Pharmacy. United States.

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## CUMPLIMIENTO: REVISIÓN DE LA EDUCACIÓN, INVESTIGACIÓN, PRÁCTICA Y POLÍTICA EN ESTADOS UNIDOS

**RESUMEN**

Objetivo: Describir la educación, investigación, practica y política relacionadas con las intervenciones farmacéuticas para mejorar el cumplimiento de la medicación en establecimientos comunitarios en Estados Unidos.

Métodos: Los autores utilizaron Medline e International Pharmaceutical Abstracts (desde 1990) para identificar los estudios de intervención de farmacia comunitaria y ambulatoria que trataban de mejorar el cumplimiento de la medicación. Los autores también buscaron en literatura primaria usando Ovid para identificar estudios relativos a la enseñanza de farmacia sobre cumplimiento de la medicación. Se revisaron las bibliografías de los estudios relevantes para identificar literatura adicional. Buscamos en los sumarios de tres revistas de educación de farmacia de Estados Unidos y se revisó la web de la Asociación Americana de Facultades de Farmacia a la busca de materiales sobre principios de educación sobre

cumplimiento. Las políticas relacionadas con cumplimiento de medicación se identificaron mediante lo que era conocido por los autores desde su experiencia profesional, asistencia a congresos y revistas farmacéuticas.
Resultados: Investigación y práctica: se identificaron 29 estudios: 18 ensayos controlados aleatorizados; 3 estudios de cohorte prospectivos; 2 estudios de cohorte retrospectivos; 5 estudios de caso control; y otro estudio. Hubo una considerable variabilidad en los tipos de intervenciones y en el uso de medidas del cumplimiento. Muchas de las intervenciones eran realizadas por farmacéuticos con formación clínica avanzada y no por típicos farmacéuticos comunitarios. Los efectos positivos de las intervenciones disminuyeron o no se mantuvieron después de que las intervenciones desaparecieron. Aunque no se evaluó formalmente, en general, las farmacias comunitarias normales no evaluaban rutinariamente y/o intervenían en el cumplimiento de la medicación.
Educación: Los grupos nacionales de educación de farmacia apoyan la necesidad de que los farmacéuticos aprendan y usen habilidades relacionadas con el cumplimiento. Los esfuerzos educativos relacionados con el cumplimiento se han centrado en el conocimiento de los estudiantes de las barreras al cumplimiento y en las habilidades de comunicación necesarias para envolver a los pacientes en un cambio actitudinal.
Política: Varios cambios en el ejercicio de la farmacia y en la legislación nacional han proporcionado a los farmacéuticos la oportunidad de intervenir y monitorizar el cumplimiento de la medicación. Algunos de estos cambios incluyeron el uso de tecnologías y la provisión de servicios especializados para mejorar el cumplimiento.
Conclusiones: Los investigadores y facultativos necesitan evaluar modelos factibles y sostenibles para los farmacéuticos en la comunidad para ayudar consistente y eficientemente a pacientes en su mejor uso de las medicaciones y mejorar sus resultados en salud.

**Palabras clave:** Adherencia a la medicación. Farmacéuticos. Educación farmacéutica. Estados Unidos.

## INTRODUCTION

Medication adherence or the older term, medication compliance, is defined as the extent to which a person's medication use behavior coincides with medical or health advice; and persistence as the duration of time from initiation to discontinuation of therapy.[1] Medication non-adherence and the lack of persistence is a severe and pervasive problem involving many not yet fully understood aspects of individual behavior and gaps in service delivery, and which often results in negative patient outcomes such as poor clinical outcomes and increased hospitalizations.[2-6] Such negative outcomes are associated with recent United States (US) healthcare costs estimated to be USD290 billion a year.[7] Research has shown non-adherence to many medications to range from 40 to 50%.[8]

After several decades of research, we have learned that medication non-adherence is due to many factors including lack of adequate knowledge about medication and treatment goals, beliefs about the medication, complex regimens that are difficult to manage, side effects, and costs associated with medications.[9-11] There have been several studies over the years showing how different interventions can improve treatment adherence.[12] In general, research shows that patient-centered, multi-modal educational and behavioral interventions are more effective than one approach.[12] Intervention approaches have included the use of various reminder systems, simplification of drug regimens, medication counseling, and collaborative team approaches, involving multiple healthcare providers, as well as follow-up and monitoring.[12,13] A relatively recent systematic review indicated that simple interventions (such as a medication calendar or pillbox) improved adherence and other outcomes for short-term treatments.[13] Such effects, however, were inconsistent with less than half of the studies showing benefits. Efforts to improve adherence to chronic medications are often complex and ineffective making it hard to interpret the full benefits of treatment.

In the United States, there has been a growing literature showing that pharmacists in a variety of practice settings and across different disease states have an important role to play in medication therapy management (MTM) activities including optimization of medication adherence. Many of the studies in the last two decades have contextualized MTM activities as a part of the pharmacist's direct responsibilities for patient outcomes commonly known as "pharmaceutical care".[14] The pharmaceutical care movement has focused on the pharmacists' responsibility to care for patients' medication-related needs including adherence. The American Association of Colleges of Pharmacy (AACP) Commission to Implement Change in Pharmaceutical Education has embraced "render[ing] pharmaceutical care" as pharmacy practice's mission.[15] These ideals are further reflected by the Joint Commission of Pharmacy Practitioners (JCPP) (representing 11 US pharmacy organizations). The JCPP vision states that "pharmacists will be the health care professionals responsible for providing patient care that ensures optimal medication therapy outcomes" and that "pharmacy education will prepare pharmacists" to provide this care.[16]

In conjunction with the pharmaceutical care movement of the 1990s, US schools and colleges of pharmacy expanded their curriculums and require all pharmacy graduates to complete a six-year clinical doctoral degree (PharmD degree). This curricular expansion enabled students to learn more clinical skills and gain additional patient care experiences. Such additional skills should position all current pharmacy graduates, regardless of practice setting, to help improve patient medication use.

Before the all-PharmD graduation requirement, pharmacists with advanced clinical knowledge would often use their additional clinical skills working in institutional settings. It was generally viewed that pharmacists practicing in community settings such as community pharmacies did not have the expertise or time to follow-up and provide additional clinical services. However, the influx of doctor of pharmacy graduates into community pharmacies along with the proliferation of community pharmacy residency programs has brought about interest and participation in the provision of additional clinical services by community pharmacists. Although there is a growing database of US studies evaluating the role of pharmacists working in community pharmacies and other ambulatory settings to improve medication adherence, the present review is believed to be the first manuscript compiling and analyzing these recent studies.

Compared to other countries, the US literature on community and ambulatory pharmacist interventions to improve adherence is fairly large. Many would, however, view the literature as relatively small and agree there needs to be considerably more research done in the area. This literature also forms the foundation for both current educational efforts in the US Schools and Colleges of Pharmacy related to teaching medication adherence, and policies and practices being advanced by various local, state, and national organizations. The present manuscript will explore all these aspects by first reviewing the ambulatory and community pharmacy adherence studies, then shifting to a review of current educational efforts underway in US Schools and Colleges of Pharmacy, and ending with current policies and practices related to the community pharmacist's role in medication adherence.

**Pharmacy Interventions in Ambulatory and Community Settings**

Methodological Approach

The databases MEDLINE and International Pharmaceutical Abstracts since 1990 were searched using the following key MeSH terms "pharmacist* or community pharmacist*" and "adherence or compliance" and "United States". The asterisk indicates that multiple variations of the term were searched (i.e., pharmacist, pharmacies, pharmacists). Studies with an intervention delivered by pharmacists practicing in an ambulatory or community pharmacy setting and that measured medication adherence were included. All study designs were included. A hand search of the bibliographies of the included studies was also conducted to identify research that was not found in the database search.

If a study reported a significant adherence finding, a statement describing the finding as well as the extent of significance (such as if the p value is ≤ to 0.05, 0.01, or .001 or the presence of a confidence interval) was included. If the study reported no statistically significant difference this was stated without the statistical measure.

Results

The literature search resulted in 29 studies[17-48] including 18 randomized controlled trials, 3 prospective cohort studies, 2 retrospective cohort studies, 5 case-controlled studies, and one other study. Annex 1 lists the studies that were included as well as the setting, intervention, adherence measures, and results. All of the studies included in this review involved interventions intended to improve medication adherence. Some studies explored the improvement of adherence as the primary endpoint and other studies viewed improved adherence as an intermediate outcome leading to improved clinical outcomes.

In 38% (11/29) of the studies a change in medication adherence was not seen.[17-20,26,27,29,31,35,43,47] In 24% (7/29) of the studies, an inadequate sample size to detect differences in adherence was identified as a limitation.[19,24,25,28,29,35,43] The use of self-reported medication adherence was also problematic as baseline medication adherence was frequently higher than expected (patients often overestimate their adherence).[22,26,28,29,35,43] Higher baseline adherence reduces the potential for change in adherence in patients receiving the intervention. The interventions used in the studies varied greatly from very specific packaging to multi-modal educational and behavioral interventions. Despite these issues many studies did demonstrate a change in adherence. Forty-four percent (8/18) of the randomized controlled studies reported at least one statistically significant adherence result. These studies demonstrated that ambulatory and community pharmacists can provide services that increase medication adherence. Additional research on the specific activities that produce these results would allow them to be reproduced.

In some studies, a change in adherence was observed soon after the start of the intervention. In others, it took some time for the intervention to influence adherence. It is not clear why this is the case but we suspect that patients require time to make cognitive and behavioral adjustments during behavioral change. Three studies also demonstrated that unless the intervention was continued, the change in adherence decreased or did not persist.[33,34,36] Research is needed to identify which patients are most likely to benefit from these services and to determine the most cost-effective method of providing these services.

In sixteen of the 29 studies (55%) the interventions were delivered by clinical pharmacists practicing in ambulatory settings and employed by the institutions where the care was being provided.[17,19,20-24,26,30.32-34,36,41-43,47] Greater involvement by community pharmacists who work in retail settings is needed to provide these services to larger patient populations. Community pharmacists are in an ideal position to provide long-term adherence services as they have access to medication refill histories and have routine contact with patients. It is important to recognize that there were no known studies assessing the extent to which pharmacists in community settings routinely

assess and intervene on medication adherence. It is generally believed that the average pharmacist in the community setting does not regularly assess and intervene on medication adherence.

**Review of Educational Efforts in US Schools and Colleges of Pharmacy**

Overview

The promotion of medication adherence is one component of pharmaceutical care practice and is considered one of four basic needs that patients have related to their medications.[49] The outcomes of AACP's Center for the Advancement of Pharmaceutical Education (CAPE) support the need for practitioners skilled in medication adherence principles. Both the "pharmacy practice" and "social and administrative pharmacy" documents supplementing the CAPE outcomes specifically indicate promoting adherence under the outcome of "pharmaceutical care".[50-52] However, US schools and colleges of pharmacy have varied greatly in providing education related to medication adherence. A 2005 survey of communication skills assessed by 50 US schools and colleges of pharmacy found that only 22% of institutions assessed students on any adherence-related skills.[53] The current review aims to identify specific educational practices used by US schools and colleges of pharmacy to develop adherence promotion skills among students. The examples provided in this section are not necessarily from the same schools and colleges of pharmacy identified in the 2005 survey that assessed students on adherence-related skills. Further, these examples represent those that have been published as examples of curricular innovations to teach students about medication adherence.

Methodological Approach

After a brief Internet search, we formally searched primary literature using Ovid, combining the MeSH terms "Education, Pharmacy" and "Medication Adherence." We also searched using the combinations of "Education, Medical" and "Medication Adherence" along with "Education, Medical" and "Education, Pharmacy" combined with "Patient Compliance." We searched motivational interviewing as it is considered an important technique for clinicians to use to engage patients in changing their medication adherence behavior. Further, we reviewed the bibliographies of relevant articles in order to identify additional literature. We also searched the tables of content of three current US journals focusing on pharmacy education: American Journal of Pharmaceutical Education, the International Journal of Pharmacy Education and Practice, and Currents in Pharmacy Teaching and Learning. These journals were searched for articles related to "adherence", "compliance" and "motivational interviewing." Finally, we reviewed the AACP website for any tools or recommendations on teaching adherence principles.

Results

In the US, many of the efforts in pharmacy education to teach adherence principles have focused on exposing students to the numerous difficulties associated with adhering to a medication regimen. The teaching strategies often involve the student pharmacists consuming placebo medications (e.g., small candies) for a short period of time in order to gain a sense of what it is like to be a patient. For example, at Idaho State University, first and third year professional students are paired for four weeks.[54] The first year students play the role of patient and are "prescribed" a complex medication regimen for which the third year student provides counseling and assessment. Through this experience, specific barriers to medication use are identified and students reflect on their experience.

Similarly, Singla and colleagues at Midwestern University (Glendale, Arizona) described an educational program that brought pharmacy and osteopathic medical students together to learn about medication adherence.[55] In this experience, medical students role-played physicians with a needle-stick requiring HIV prophylaxis therapy. The pharmacy students then provided patient counseling and an assessment of adherence. This activity was four weeks in duration and many barriers to adherence were discussed. Also focusing on regimens for HIV, faculty at West Virginia University designed a program to expose pharmacy students to the difficulties associated with adhering to antiretroviral therapies.[56] Students took placebos for one week, similar to the other studies described above, and recorded their adherence on a log sheet. The students reported many common barriers to medication adherence. Finally, Divine and colleagues reported on an adherence simulation program at the University of Kentucky that involved students using multiple "medications" for 10 days in order to better understand the experiences of geriatric patients.[57]

There appear to be limited published examples of programs in pharmacy education designed to specifically develop student communication skills that promote adherence. One example is from Auburn University, a pharmacy school with experts in motivational interviewing. As described by Villaume and colleagues, "treatment nonadherence results from patient ambivalence and resistance".[58] At Auburn, educators have created the "Auburn University Virtual Patient." This program allows students to consider each part of a patient-pharmacist interaction and reflect on how the success of the conversation is impacted by what is said by the pharmacist. During the prototype stage of the Virtual Patient program, students created "scripts" for the Virtual Patient, including Virtual Patient responses and how the student would respond using both motivational interviewing techniques and a traditional "biomedical" approach. These exercises help the students understand how effective/ineffective conversations unfold and how such conversations impact patient outcomes.

Another recent paper described the use of standardized patients or actors in a communication

skills course and lab as a way for students to actively learn how to counsel patients who are non-adherent to drug therapy.[59] Students were given medication profiles reflecting non-adherence to a drug therapy. The students were expected to detect, assess, and intervene on the medication non-adherence. The standardized patients were given scripts to indicate, when elicited from the student, various issues they were having with the medications. Students were given these same scenarios at the beginning and end of the course. Using a structured communication skills assessment form, students' communication skills were assessed during both times. The educators used the changes in the evaluation form at the beginning and end of the course as a way to assess student learning on how to effectively intervene using communication skills on patient non-adherence.

Although a review of the literature revealed a small number of published examples describing teaching approaches to engaging more students in medication adherence assessment and intervention techniques, further educational research is warranted. It is reasoned that the more students practice such approaches before they graduate, the more likely they will engage in such activities when practicing as pharmacists.

**Current Policies and Practices Related To Pharmacy Medication Adherence Activities**

Methodological Approach

Policies related to medication adherence were identified based on what was commonly known to the authors from professional experience, attendance at professional meetings, and pharmacy journals. The authors did not employ any specific electronic literature database(s) or other formal mechanism to ascertain current policies related to medication adherence.

Results

There have been several policies and practices over the last three decades that support the role of the US pharmacist in community settings to engage in adherence interventions. For over two decades, most community pharmacies have maintained computerized prescription profiles that allow them to identify late refills. These computerized profiles are only appropriate estimates of refill patterns when the patient only uses the pharmacy or chain of pharmacies (assuming the particular chain pharmacies have linked computer systems). If the patient goes to multiple pharmacies, gaps in their profiles may inaccurately reflect non-adherence. Many of the computer software programs also have capabilities to display electronic messages indicating the patient is late in picking up refills. Unfortunately, the busyness of most community pharmacy practices makes it difficult for pharmacists to consistently engage patients when they see these messages pop up on their screens.

Large chain pharmacies have also recently implemented tools and programs to improve adherence. For example, several of the large pharmacy chains have tools on their company websites in which patients can sign up and have reminders to take their medications sent electronically to their cell phones, home/office numbers, and e-mail addresses. Some of the chains have telephone-based programs to call patients when they are late in picking up their medications and simply remind them to pick up their medications. Nearly all community pharmacies sell pillboxes that can help patients remember when to take their medications. Select and perhaps more progressive pharmacies collect fees for packaging a patient's monthly medications into boxes or blister packs. Some pharmacies have attempted to synchronize the prescription refills for patients. This helps the pharmacy by making the workload more predictable and ensures that the patient has needed medications.[60] There are also several companies that have started up to help pharmacies identify patients such as those non-adherent requiring additional and personalized services. Mirixa[61], PurpleTeal[62], Aprexis Health Solutions[63], Outcomes Pharmaceutical Health Care[64], and Medication Management Systems, Inc.[65] are just a few examples of new companies focused on helping pharmacists provide adherence services.

In addition to pharmacy-driven initiatives to improve adherence, there have been some efforts by federal and state governments for community pharmacists to improve adherence. At the federal level, the passage of the US Medicare Modernization Act of 2003 and the Medicare Prescription Medication Benefit (Part D) formally marked the initiation of Medication Therapy Management (MTM) services for patients enrolled in Medicare, a federal program providing medical and prescription coverage for older adults.[66] The Centers for Medicare and Medicaid Services describe MTM as a means to ensure that "medications prescribed for targeted beneficiaries are appropriately used to optimize therapeutic outcomes and reduce the risk of adverse events".[67] MTM has been further defined by the profession as "a distinct service or group of services that optimize therapeutic outcomes for individual patients [that] are independent of, but can occur in conjunction with, the provision of a drug product".[68]

The American Pharmacists' Association and the National Association of Chain Drug Stores Foundation provide further guidance by defining the "core elements" of an MTM service, including medication therapy review, personal medication record, medication action plan, intervention and/or referral, and documentation and follow-up.[69] While the "core elements" serve as a basis for all MTM services, the mechanisms to enroll patients and to provide compensation to the pharmacist to care for the patient differ based on the payer.

In 2009, an average of 13% of patients receiving Medicare was provided MTM.[69] Each individual Medicare insurance plan has unique criteria for MTM enrollment. Eighty-four percent of plans required the beneficiary to be taking two to five Medicare-covered medications and be treated for two to three chronic diseases.[70] The five most

common chronic conditions were diabetes, heart failure, hyperlipidemia, COPD and hypertension.[70] Additionally, a further criteria for enrollment was that the total medication costs, as paid by both patients and insurers, was over USD4000 a year for medications.

The most common mechanisms to provide care and contact with the patient were: medication reviews, phone outreach, face-to-face contact, refill reminders, intervention letters, educational newsletters, prescriber consults, drug interaction screenings, case management and medication profiles or lists.[70] While patient adherence is not currently a required outcome marker of Medicare, it can be inferred from the types of patient contact that it is a component of most of the Medicare-supported MTM programs. The payments for the provision of MTM is unique to each Medicare insurance plan with the majority of plans using in-house staff.[70,71] Examples of MTM programs and networks that engage community-based pharmacists in the provision of MTM to Medicare beneficiaries include: Humana[72], Mirixa[61], and Outcomes Pharmaceutical Health Care.[64] The use of community-based pharmacists is likely to increase during the 2010 calendar year because the new requirements for MTM programs are that the services must be delivered face-to-face.[73]

At the state level, some states for many years have been reimbursing pharmacists for adherence activities provided to patients receiving state prescription coverage due to having a low income and other eligibility requirements (called Medicaid).[74] More recently, individual state Medicaid programs have also partnered with pharmacists to provide MTM to their beneficiaries. Select states that are known to have MTM programs which engage community-based pharmacists include: Iowa, Minnesota, North Carolina, Florida, Mississippi, Montana, Ohio, Vermont, and Wyoming.[75] As with Medicare MTM programs, adherence is not a required outcome measure in all of these programs, but the programs do generally identify patients with multiple medications and multiple chronic conditions. There are a number of additional states with programs starting and advocacy for such programs underway. A common theme between most of the programs is they were established with a partnership of the state pharmacists association, the schools or colleges of pharmacy located within the state, and the state Medicaid program.

Aside from these efforts, several foundations, pharmaceutical companies, and federal agencies (such as the National Institutes of Health) have provided researchers grants to explore and evaluate adherence interventions by community pharmacists. The Pharmacy Quality Alliance (PQA), a non-profit organization, has developed a collaborative program focused on improving the quality of medication use across multiple health settings.[76] One of their many initiatives has been examining through pilot research the use of adherence measures as a benchmark for the quality of community pharmacies. Such initiatives are controversial as they assume that pharmacies should be responsible for patient medication adherence behaviors. Many community pharmacists feel they can't be responsible for a patient's rational decision to not take their medications as prescribed. Others say that pharmacists should be responsible for adherence outcomes if one supports the philosophy of pharmaceutical care and pharmacists being directly responsible for patient drug therapy outcomes. One potential consequence of this work is that adherence measures are created for each pharmacy and publicly reported as an index for each pharmacy's quality of care. Clearly, more research will need to be conducted before all can accept adherence measures as a benchmark for pharmacy quality.

## CONCLUSIONS

The present review describes several trials showing the impact of pharmacists in community settings on patient adherence. While a majority of studies show pharmacists having a significant impact on medication adherence, there are several as well showing the lack of an impact on adherence. In some cases, the lack of impact may be due to sample size and study design issues. It is not clear how well researchers assessed the consistency to which the interventions were carried out (program fidelity) and may account for some of the decreased impact. It is also not clear how many of the interventions described are sustainable and being actively maintained in practice.

The practice model used for many of the interventions in the review involved face-to-face visits via appointments. Due to heavy prescription volumes associated with most US pharmacies, it seems impractical to expect appointment-based care to be the sole model of adherence interventions. Telephone-based adherence management was another model explored and could better fit into current practice patterns as calls could be made during slower times. This latter approach is still fraught with problems as it is not always clear when to consistently plan calls, and patient availability often does not match pharmacist availability. In these latter "in-house" (at the pharmacy site) models of adherence intervention and monitoring, it is also likely additional pharmacy staff may need to be hired to offset the time given for such adherence initiatives. Such additional costs may not be feasible for many US pharmacies struggling to maintain profits given heavy competition and lean reimbursements from insurance companies. Further, to survive financially, community pharmacists need to be reimbursed for their time (face-to-face or via telephone) in helping patients manage their medications. Reimbursement efforts at the federal and state level as described previously are helpful and making it more possible for community pharmacists to engage in these activities without incurring financial hardships. Similar efforts are also needed by private insurance payers in compensating pharmacists for their services.

There needs to be more research to explore other models for which pharmacists in community settings can consistently and actively engage in adherence interventions and monitoring. One model currently being explored by the lead author of this review involves pharmacists at an off-site location making outbound calls to patients regarding ways to improve adherence. The primary disadvantage of the model is the difficulty for patients to establish a relationship with a pharmacist they do not know over the phone. However, the key advantage of the model is that it avoids the point-of-service and economic demands of prior models.

Future research should not only test these latter models for feasibility and effectiveness but also explore how pharmacists can approach adherence interventions and monitoring at the population level. For example, are there tools or algorithms that can be developed that allow pharmacists to stratify individuals based on degree of risk for non-adherence and that the nature and extent of interventions be based on patient's degree of risk? We need such tools to help pharmacists in community settings efficiently deliver the right dose of patient-centered interventions to those in need. Therefore, research is needed to identify the resources and models of practice best to provide these services in a community pharmacy setting. Additional educational research is warranted to identify effective strategies for preparing pharmacists to assist patients in medication adherence. It is clear that by delivering efficient and effective adherence interventions, US pharmacists in community settings can have a significant and cost-effective impact on improving the health of our communities.

**CONFLICT OF INTEREST**

None declared.

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| **Annex 1.** | | | | | |
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| **Study** | **Condition** | **Methods** | **Intervention** | **Adherence Measure** | **Adherence Outcomes** |
| ***Randomized Controlled Trials*** | | | | | |
| *Hypertension* | | | | | |
| 17. Carter BL et al. (2008) | Hypertension | • N=179<br>• Intervention clinics vs. control clinics<br>• 9 months<br>• 5 clinics within 15 miles of Iowa City, IA<br>• Clinical Pharmacists | Identified suboptimal medication regimens, recommended adherence aids and negotiated strategy with patient to improve adherence | Medication adherence at 9 months calculated from pill counts as the percent of predicted doses measured at each study visit | • Significantly greater adherence at baseline in control group (89% vs. 71%, p<0.001)<br>• Only 4% of recommendations involved adherence<br>• No difference in adherence at 9 months (92% in control group vs. 94% in intervention group) |
| 18. Planas LG et al. (2009) | Hypertension | • N=52<br>• Pharmacist intervention vs. Control<br>• 49months<br>• 5 community pharmacies in Tulsa, OK<br>• Community Pharmacists | Provided medication therapy management services including education on medications, identification and resolution of drug therapy problems, adherence assessment and personalized plans as needed | Adherence measured from claims history provided by the managed care organization using a medication acquisition method | Mean adherence during study period (control vs. intervention 78.8% vs. 87.5%, p=ns |
| 19. Mehos BM et al. (2000) | Hypertension | • N=36<br>• Control vs. Pharmacist Intervention<br>• 6 months<br>• Family medicine residency training clinic in Denver, CO<br>• Clinical Pharmacists | Gave blood pressure monitor and performed monthly telephone calls to evaluate blood pressure response | Percent adherence calculated by dividing the number of tablets/capsules refilled by the amount prescribed during the study | Change in adherence not seen: Control: 89% vs. Intervention: 82% |
| *Elderly Patients* | | | | | |
| 20. Hanlon JT et al. (1996) | Elderly patients with 5 or more regularly scheduled medications | • N=208<br>• Usual care vs. usual + clinical pharmacist care<br>• 1 year<br>• General Medicine Clinic in Durham, NC<br>• Clinical Pharmacists | Encouraged patient adherence using both adherence-enhancing strategies (reminder packages/calendars) and written patient education materials | Self-reported: the proportion of medications for which patients' response agreed with the directions for their use. This approach was chosen based on a study showing the self-reported medication use and actual use were comparable in elderly patients. | Adherence: No statistically significant change Intervention: 77.4% vs. Control: 76.1% |

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| 21. Lee JK et al. (2006) | Elderly patients with at least 4 chronic medications | • N=200<br>• Pharmacy Care (PC) vs. Usual Care (UC) in 3 phases<br>• 14 months<br>• Medical center in Washington, DC<br>• Clinical Pharmacists | Individualized medication education, medications dispensed using an adherence aid, and regular follow-up for 6 months. Half were randomly selected for an additional 6 months of intervention. | • Proportion of pills taken from blister packs on months 4, 6, 8, 10, 12, and 14 measured by pill counts<br>• Primary outcome: change in medication adherence | • Mean adherence (%):<br>Baseline: 61.2<br>8 month for PC group 96.9 (p<0.001)<br>14 month UC 69.1 vs. PC 95.5 (p<0.001)<br>• ≥80% adherent (%):<br>PC @ 14 months: 97.4<br>UC @ 14 months: 21.7 (p <0.001) |
| *HIV/AIDS* | | | | | |
| 22. Rathbun, RC et al. (2004) | HIV/AIDS[a] | • N=33<br>• Adherence clinic (AC) vs. standard care (SC)<br>• 7 months<br>• HIV clinic in Oklahoma City, OK<br>• Clinical Pharmacists | Educated about appropriate administration of HAART[b], food restrictions, adverse event management strategies, and monitored patient progress after therapy initiation with follow-up as needed | Electronic monitoring device used to measure:<br>• Medication consumption (number of doses consumed divided by number of prescribed doses)<br>• Dose precision (percent of doses taken at the prescribed interval calculated by number of doses taken within 1.5 hours of interval divided by total number of prescribed doses)<br>• Self-reported adherence using a validated, 2-page questionnaire to assess adverse events, patient perception of treatment, and adherence during the preceding week. Was administered at weeks 4,16, and 28. | • Medication consumption AC vs. SC:<br>Week 4: 86% vs. 73%<br>Week 16: 77% vs. 56%<br>Week 28: 74% vs. 51%<br>• Dose Precision (AC vs. SC):<br>Week 4: 69% vs. 42%, (p< 0.05)<br>Week 28: 53% vs. 31%, (p< 0.05)<br>• Self-reported adherence*: (AC vs. SC) 94% vs. 89% |
| *Depression* | | | | | |
| 23.& 24. Finley PR et al. (2002 & 2003) | Depression | • N=125<br>• Collaborative care model group vs. Control group<br>• 6 months<br>• Medical Center in San Rafael, CA<br>• Clinical Pharmacists | Titrated medication doses with scheduled follow-up appointments and telephone calls to assess drug adherence and drug therapy | • Medication possession ratio (MPR) from computer refill records defined as the number of days supply of drug the patient received over the 6-month period | Pilot Project<br>• MPR (intervention vs. control): 6 months: 0.811 vs. 0.659, (p<0.005)<br>• Percent continuing therapy beyond 3 months (intervention vs. control): 0.811 vs. 0.659 (p< 0.005)<br>Study<br>• MPR (intervention vs. control) at 6 months: 0.83 vs. 0.77 |

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| 25. Rickles N et al. (2005) | Depression | • N=63<br>• Telemonitoring group (PGEM) vs. Usual Care (UC)<br>• 6 months<br>• 8 community pharmacies in Wisconsin<br>• Community Pharmacists | Placed 3 monthly telephone calls to assess knowledge of antidepressants, adverse effects, and treatment goals | Percent non-adherence measured from pharmacy records and self-report of adherence within past 7 days. Patients were asked to answer the question "in the past 7 days ending yesterday, how many times did you miss taking a pill?" which is based off of an item in the validated Brief Medication Questionnaire. | • Percent non-adherence at 6 months (PEGM vs. UC): 30.3 vs. 48.6 ($p \leq 0.05$)<br>• Self-reported adherence: no difference between groups |
| 26. Capoccia KL et al. (2004) | Depression | • N=74<br>• Enhanced care vs. Usual care<br>• 1 year<br>• University of Washington Medical Center<br>• Clinical pharmacist | Provided weekly telephone calls for the first 4 weeks, followed by phone contact every 2 weeks through week 12, then every other month from months 4-12 to address depressive symptoms and medication-related concerns | Medication adherence measured by self-reported number of days taking antidepressant medication in past month (percent of patients adherent ≥ 25 days/past 30 days), which has shown excellent agreement between questions regarding the use of antidepressants in the past month and refill records in previous studies. | No change in adherence between groups |
| *Asthma and COPD* | | | | | |
| 27. Weinberger M et al. (2002) | Asthma and COPD[c] | • N=447<br>• Control (C) vs. usual care (UC) vs. pharmaceutical care (PC)<br>• 1 year<br>• 36 Indianapolis chain drugstores<br>• Community Pharmacists | PC: Provided techniques to measure peak flow, study materials, handouts, and resources, and reinforced adherence. PEFR values were reported during monthly phone calls to research personnel.<br>UC: Patients received neither peak flow meters nor instructions on their use<br>C: Patients received peak flow meters and instructions on their use but PEFR values were not reported to pharmacist | Proportion of non-adherence over the previous month using:<br>• Inui self-reporting instrument<br>• Morisky 4-item scale | No difference in self reported adherence* |
| *Helicobacter Pylori Infection* | | | | | |

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| 28. Lee M et al. (1999) | Helicobacter pylori infection | • N=125<br>• Enhanced compliance program (ECP) vs. control group<br>• 14 days<br>• 4 ambulatory health centers in MA<br>• Pharmacists | Provided initial counseling, written information, demonstrated medication calendar and pillbox, and made follow-up telephone calls at least 3 days after therapy initiation | Numbers of patients able to complete 60% or more and 90% or more of the 2-week regimen based on pill counts | • No difference in percent of patients taking > 60% of medication (ECP vs. control): 95 vs. 89<br>• Percent of patients taking > 90% of medication (ECP vs. control): 89 vs. 67 ($p<0.01$) |
| 29. Stevens VJ (2002) | Helicobacter Pylori infection | • N=333<br>• Usual care vs. counseling and follow-up<br>• 3 months<br>• Health Maintenance Organization in Portland, OR<br>• Pharmacists | Provided 15 minute counseling sessions including side effects, importance of completing regimen, possible barriers to adherence and coping strategies, follow-up call 2-3 days after start to check on adherence. Participants were then contacted 8 days after start of medication regimen and asked to report adherence to the current regimen and symptoms. | Self-reported percent of participants missing ≥1 doses of each component of the regimen measured 8 days after treatment start. The questionnaire used was not validated. | No difference in percentage of patients missing any component of the regimen |
| *Diabetes Mellitus* | | | | | |
| 30. Odegard PS et al. (2005) | Diabetes Mellitus | • N=77<br>• Usual care vs. Pharmacist intervention<br>• 1 year<br>• 8 clinics in the greater Seattle, WA area<br>• Clinical Pharmacists | As part of a diabetes care plan, conducted weekly in-person or telephone meetings then monthly after predetermined progress with plan was reached | Self-reported: number of missed medication doses over the last 2 weeks using 2-question recall technique validated in a chronic disease model. | • Percent of patients reporting missing medication doses (intervention vs. control): 56 vs. 35<br>• Self-reported adherence* in pharmacist intervention group was not better than usual care group |
| 31. Grant RW et al. (2003) | Diabetes Mellitus | • N=232<br>• Pharmacist intervention vs. control<br>• 3 months<br>• Community health center near Boston, MA<br>• Pharmacists | Addressed adherence and adherence barriers via initial phone interview, performed assessment of adherence, and provided drug-specific education, sent E-mail to primary care provider summarizing discrepancies and adherence barriers | Self-reported adherence measured as number of adherent days out of past 7 days, which has shown in prior research to have a good correlation with electronic monitoring. | Self-reported adherence* rates high at baseline for both groups and did not change |
| *Other Chronic Medications* | | | | | |

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| 32. Solomon DK et al. (1998) | Hypertension and COPD[c] | • N=231<br>• Traditional pharmacy care vs. pharmaceutical care<br>• 6 months<br>• 10 Veteran's Affairs medical centers and 1 university hospital throughout the United States<br>• Clinical Pharmacy Residents | Focused on symptom control, patient adherence, drug product selection, use of resources, patients' satisfaction with care, disease and disease management knowledge, and quality of life issues in 6 monthly visits | • Four item self-reported adherence measure by Morisky et al.<br>• Tablet counts when medications were brought to visits | • Hypertension<br>Self-reported adherence* (treatment vs. control): 0.23 vs. 0.61 (p< 0.05)<br>• COPD<br>No change in self-reported adherence (no data provided)<br>• Tablet count results not provided. |
| 33.& 34. Murray MD et al. (2007 & 2004) | Heart Failure | • N=314<br>• Pharmacist intervention (PI) vs. Usual care (UC)<br>• 1 year<br>• Inner-city ambulatory care practice in Indianapolis, IN<br>• Clinical Pharmacist | Nine-month pharmacist intervention provided patient-centered verbal instructions and written materials about medications and monitored patients' medication use, healthcare encounters, and body weight, followed by 3-month follow-up period. | • Medication adherence tracked by using electronic monitors to compute taking adherence and scheduling adherence<br>• Refill adherence measured by medication possession ratio (medication received relative to amount prescribed) obtained from prescription records<br>• Self-reported adherence using Inui and Morisky questionnaires | • At end of intervention (UC vs. PI):<br>Taking adherence: 67.9% vs.78.8% (CI 5.0-16.7)<br>Scheduling adherence: 47.2% vs. 53.1% (CI 0.4-11.5)<br>• After 3 month follow-up period (UC vs. PI):<br>Taking adherence: 66.7% vs. 70.6% (CI -2.8-10.7)<br>Scheduling adherence: difference 48.6 vs. 48.9 (CI -5.9-6.5)<br>• 1 year refill adherence: 105.2% vs.109.4% (p< 0.05) |
| **Error! Bookmark not defined.** Nietert PJ et al. (2009) | Chronic Disease Medications | • N=3048<br>• Patient telephone (PP) contact vs. Physician fax contact (FP) vs. usual care (UC)<br>• 9 months<br>• 9 pharmacies within a medium-sized grocery store chain in South Carolina<br>• Community Pharmacists | (PP) arm provided telephone calls to overdue patients asked why, reminded them on importance of taking medication, and helped the patient find ways to overcome barriers. (FP) arm provided physicians with written prompts to assist patients with persistence | Refill persistence from administrative pharmacy data identifying patients who were ≥ 7 days overdue (index date) and defined as number of days from index date to next date of next prescription refill | No significant difference in adherence by treatment arm |
| 36. Faulkner et al. (2000) | Patients undergoing coronary artery revascularization and on lipid lowering therapy | • N=30<br>• Telephone contact vs. no telephone contact<br>• 2 years<br>• Cardiac Clinic in Omaha, NB<br>• Clinical pharmacist | Telephoned patients weekly for 12 weeks - Emphasis placed on importance of therapy, and patients questioned on specific reasons for non-adherence when applicable | Non-adherence defined as<br>• Short term: Returning >20% of prescribed pills at week 6 and 12 visits (pill and packet counts)<br>• Long term: Failing to fill ≥ 80% of prescriptions at 1 and 2 years (pharmacy refill records) | • Short term adherence: No significant difference<br>• Long term adherence: 63% telephone contact vs. 39% no telephone contact for lovastatin 48% telephone contact vs. 23% no telephone contact for colestipol (p<0.05) |
| ***Prospective Cohorts*** | | | | | |

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| *Tuberculosis* | | | | | |
| 37. Tavitian SM et al. (2003) | Latent Tuberculosis Infection (LTBI) | • N=294<br>• No control group<br>• 8 years<br>• Ambulatory care health center in Los Angeles, CA<br>• Clinical pharmacists | Pharmacist managed clinic for hospital employees with LTBI. First visit included discussion of importance of adherence, then by appointment at months 1, 2 and 3 to reinforce<br>Telephone interviews on months 4-9. Non-adherent patients were telephoned 2-4 times a month until reached | Completion rate determined by number of health care workers who completed course of LTBI therapy divided by number of workers monitored in the clinic | Pharmacists managed clinic improved treatment completion rates. (Authors finding no statistical data provided) |
| *Chronic Medications* | | | | | |
| 38. Berringer R et al. (1999) | Diabetes Mellitus | • N=3867<br>• No control group<br>• 1 year<br>• 2 independently owned community pharmacies in Richmond, VA<br>• Community Pharmacists | Monitoring by staff pharmacists including patient education, patient concerns at point-of-dispensing<br>Chart review by staff and clinical pharmacists. | Medication adherence rate calculated by dividing actual days supply by the prescribed days supply using prescription refill records | • Mean adherence rates:<br>Year prior to program: 88.1% ± 19.1%<br>• During study year: 90.3% ± 16.3% |
| 39.& 40. Bluml et al. (1998 & 2000) | Hyperlipidemia | • N=397<br>• No control group<br>• Average period of 24.6 months<br>• 26 community pharmacies & ambulatory care pharmacies in 12 states<br>• Community and clinical Pharmacists | Collaborative practice model including private/semiprivate consultation areas, technician support, documentation systems, and point-of-care testing technologies. Follow-up visits scheduled every month for 3 months then quarterly thereafter | Number of patients who did not miss doses for ≥ 5 days or miss a scheduled refill visit by more than 5 days divided by total number of patient visits | 90.1% adherence rate at end of study |
| ***Retrospective Cohorts*** | | | | | |
| *HIV/AIDS*[a] | | | | | |

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| 41. Gross R et al. (2005) | HIV/AIDS[a] | • N=110<br>• 3 refill mechanisms: monthly pick-up at hospital pharmacy vs. monthly mail order vs. pharmacist-dispensed pill organizers every 2 weeks<br>• 3 months<br>• VA Medical Center HIV clinic in Philadelphia, PA<br>• Clinical pharmacists | Dispensed pill organizers to patients with suspected or documented poor adherence every 2 weeks, telephoned if prescriptions were not picked up at drop-off/mail order pharmacies | Adherence over previous 3 months defined as: (the number of pills dispensed divided by number of pills prescribed per day)/(number of days between refills) multiplied by 100<br>Good adherence defined as 85% or greater | • Percent Adherence:<br>Mail order vs. pick up: 91 vs. 80 ($p< 0.05$)<br>Pill organizer vs. pick up: 99 vs. 80 ($p< 0.05$)<br>Mail order vs. pill organizer: 91 vs. 99 ($p=0.14$)<br>• Proportion w/ good adherence:<br>Mail order vs. pick-up: 61% vs. 39% ($p < 0.05$)<br>Pill organizer vs. pick-up: 100% vs. 39% ($p<0.001$)<br>Mail order vs. pill organizer: 61% vs. 100% ($p< 0.05$) |
| *Tuberculosis* | | | | | |
| 42. Hess K et al. (2009) | Latent Tuberculosis infection (LTBI) among college students | • N=348<br>• No control group<br>• 9 months<br>• LTBI Clinic in CA university<br>• Clinical Pharmacists | Counseled on importance of treating LTBI and encouraged patients to complete therapy | Successful completion: taking 270 tablets in a 9-12 month period<br>6-month completion: taking 180 tablets in a 6-month period<br>Assessed by pharmacists' counts or self-reported if vial not available | • Successful completion rate 6 month: 67% vs. 9 month: 59% |
| ***Case Controlled Studies*** | | | | | |
| *Hypertension* | | | | | |
| 43. Vivian EM (2002) | Hypertension | • N=56<br>• Pharmaceutical care group vs. control group<br>• 6 months<br>• Veteran's Affairs Medical Center in Philadelphia, PA<br>• Clinical Pharmacists | Provided drug counseling and hypertensive drug therapy changes during monthly visits | Non-adherence: Percent forgetting to take at least 1 dose within past week (self-reported using a questionnaire that was not validated) or failure to refill drugs within 2 weeks after the scheduled refill date (refill records) | No significant difference in adherence |
| *HIV/AIDS[a]* | | | | | |
| 44. Visnegarwala F et al. (2006) | HIV /AIDS[a] in HAART naïve women | • N=74 women<br>• Adherence Coordination Services (ACS) group vs. Directly Delivered Therapy (DDT) group vs. Standard of Care (SoC) group<br>• 6 months duration<br>• HIV clinic in Houston, TX<br>• Pharmacists | ACS group received reminder calls for pharmacy refills. DDT had medications delivered to them | 7-day self-reported adherence for ACS group using a self report questionnaire and number of empty bubble packs for DDT group | Adherence; ACS: 81% of 11 women on HAART had 100% self-reported adherence. DDT: 85% average level of adherence. SoC: Not measured |

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| 45. Hirsch JD et al. (2009) | HIV/AIDS[a] | • N=1353<br>• Pilot pharmacy group vs. other pharmacy group<br>• 1 year<br>• 10 HIV/AIDS specialty community pharmacies in CA<br>• Community Pharmacists | Managed adverse drug reactions and side effects, evaluated patients' ability to adhere to medication regimens, tailored drug regimens to accommodate specific patient needs | Medication possession ratio equal to the sum of the number days supply of ART medication for 1 year divided by 365.25 days<br>• Non-adherent: <50%<br>• Partially adherent: 50-79%<br>• Adherent: 80-120%<br>• Excess fills: >120% | Adherent (Pilot vs. Other):<br>Non-adherent: 12.3 vs. 9.3 (p=0.001)<br>Partially adherent: 11.7 vs. 7.8 (p<0.001)<br>Adherent: 56.3 vs. 38.1 (p<0.001)<br>Excess fills: 19.7 vs. 44.8 (p<0.001) |
| 46. Lentz N et al. (2007) | HIV/AIDS[a] | • N=50<br>• Refill Assistance Monitoring Program (RAMP) vs. non-RAMP<br>• 6 months<br>• BioScrip Pharmacy in Milwaukee, WI<br>• Community pharmacists | Implemented RAMP, a telephone-based refill reminder program where the pharmacy contacted patients 5 days before their medications were due to assess medication management issues and schedule the refill and delivery of medication | Medication Possession Ratio (MPR) measured by pharmacy refill records calculated by dividing the total number of days supply for all fills minus the days supply of last fill by the number of days between first and last fill | • Mean MPR's:<br>RAMP: 1.03 vs. Non-RAMP: 0.86<br>• >=85% adherence rates:<br>RAMP: 96% vs. Non-RAMP: 60%<br>• >=95% adherence rates:<br>RAMP: 92% vs. Non-RAMP: 32% |
| *Other Chronic Medications* | | | | | |
| 47. Bozovich et al. (2000) | Hyperlipidemia | • N=205<br>• Lipid clinic vs. control group<br>• 6 months<br>• Lipid clinic in Greensboro, NC<br>• Clinical Pharmacists | 60 minute initial visit which included evaluation of barriers of adherence, followed by weekly 30-minute visits for reinforcement | Percent adherence defined as refilling a prescription within 3 days of when it was due to be refilled, measured by direct patient questioning and analysis of local pharmacy refills | • 80% adherence with drug changes and laboratory visits at 9 months.<br>• Medication adherence was not reported separately from laboratory visit compliance. |
| ***Other*** | | | | | |
| *Hypertension* | | | | | |
| 48. Lai LL (2007) | Hypertension | • N=103<br>• No control group<br>• 9 months duration<br>• Community pharmacy in South Florida<br>• Community Pharmacists | Community pharmacy-disease management program where pharmacist measured blood pressure, provided consultation to patients | Percent of patients who refilled medications on time. | • Percent of patients getting refills on time at: 1 month: 71.2%, 3 months 82.7%, 6 months 88.5%, 9 months 95.7%<br>• Compared to baseline 70.6%, after 9 months 95% of participants renewed their prescriptions on time (p< 0.05) |

a. Human Immunodeficiency Virus/ Acquired Immune Deficiency Syndrome
b. Highly active anti-retroviral therapy
c. Chronic obstructive pulmonary disease
*Self-reported Adherence via a validated method