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Moving from the Trial to the Real World: Improving Medication Adherence Using Insights of Implementation Science

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Abstract

Medication nonadherence is a serious public health concern. Although there are promising interventions that improve medication adherence, most interventions are developed and tested in tightly controlled research environments that are dissimilar from the real-world settings where the majority of patients receive health care. Implementation science methods have the potential to facilitate and accelerate the translation shift from the trial world to the real world. We demonstrate their potential by reviewing published,

high-quality medication adherence studies that could potentially be translated into clinical practice yet lack essential implementation science building blocks. We further illustrate this point by describing an adherence study that demonstrates how implementation science creates a junction between research and real-world settings. This article is a call to action for researchers, clinicians, policy makers, pharmaceutical companies, and others involved in the delivery of care to adopt the implementation science paradigm in the scale-up of adherence (research) programs.

Medication adherence:

the process by which patients take their medication as prescribed, which consists of three interrelated phases: initiation, implementation, and persistence

Implementation science:

the study of methods to promote the integration of research findings and evidence into health care policy and practice

PROBLEM STATEMENT

As the prevalence of patients with chronic conditions grows, patients worldwide are increasingly reliant on multiple medications to control their disease (1). Patients who are not taking medications as prescribed are at an elevated risk for complications, potentially leading to increased hospitalizations and mortality (2). In addition to the negative clinical impact of medication nonadherence, its economic impact is substantial. In the United States, medication nonadherence is associated with 125,000 deaths annually, at least 10% of hospitalizations, and \$100–290 billion in potentially avoidable health care spending (3). Health care costs associated with nonadherence are on the rise; a recent report estimated the cost of medication nonadherence at \$564 billion annually in the United States (4). In Germany, the total (direct and indirect) cost of medication nonadherence equals the cost for treatment of cardiovascular disease (5). As a result of these clinical and cost burdens, medication nonadherence represents a major public health threat, and there is a need for targeted, implementable solutions.

Defining Medication Adherence

Medication adherence is defined as the process by which patients take their medications as prescribed. The ABC taxonomy suggests that there are three interrelated phases: initiation, implementation, and persistence (Figure 1) (6). Each phase has its own characteristics and specific considerations in view of operational definitions and measurement, assessment of correlates or determinants, and implementation of preventative and/or remediating interventions. Initiation refers to the moment when a patient takes the first dose of a new medication regimen, typically after having received a prescription. The implementation phase, which is distinct from the concept

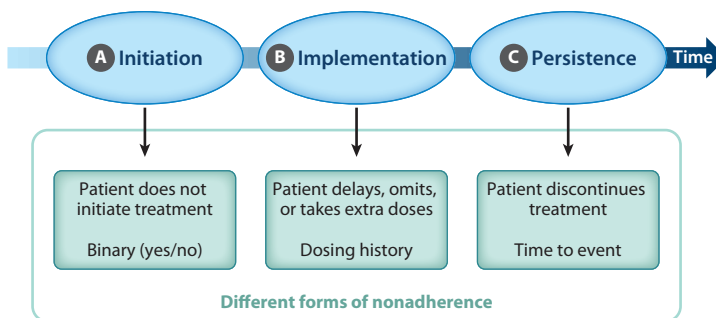


Figure 1

The ABC taxonomy of medication adherence.

of implementation science, refers to “the extent to which a patient’s actual dosing corresponds to the prescribed dosing regimen, from initiation until the last dose is taken” (6, p. 696). Persistence refers to the time that patients remain on the prescribed drug regimen from initiation until discontinuation (6).

The main drivers in medication nonadherence are typically noninitiation and discontinuation (7). Noninitiation rates vary between health care systems and contexts. For example, noninitiation rates are estimated at 15% in Spain (8), at 13.1% in Estonia (9), and between 22% and 26% in the United States (10, 11). About half of the patients initiating a medication regimen discontinue after one year (12). This proportion varies among medication regimens, with antidepressants having the highest rate of discontinuation (7). During the implementation phase, adherence may be suboptimal because of issues related to taking medications daily, the specific timing of doses, drug holidays (e.g., structured periods of purposefully not taking a medication), dose alterations, or incorrect food combinations with medication administration. Adherence problems at the implementation phase occur in about 10% to 15% of patients (13).

Context: the environment or setting in which patients receive health care

Behavioral intervention: interventions or programs designed to impact a patient’s actions regarding their personal health

Challenges with the Adherence Interventions Evidence Base

Despite increasing efforts to develop and test interventions supporting adherence, a strong evidence base for approaches to improving medication adherence is lacking. Several limitations contribute to this lack of evidence.

First, most interventions are inappropriately targeted or nonspecific. Many interventions do not clearly state which of the three phases of medication adherence they are targeting. For example, issues with discontinuation, typically the result of rational decision making by the patient, need different interventions than issues in the implementation phase, which are often the result of forgetfulness or disruption of routines. Thus, interventions that target attitudes and knowledge might be more helpful in the case of discontinuation. Reminder systems have more value during the implementation phase, although rational decision making might also drive nonadherence during the implementation phase. The current array of tools available to clinicians and researchers is not sufficiently specific to target solutions to adherence phase(s) or barriers.

Second, despite increasing evidence indicating the need for multilevel interventions, most adherence interventions focus exclusively on the patient level (14–21). There is a need for interventions that also target health care providers, organization of health care delivery, and health care systems (22–24) that are coupled with an awareness of the larger health policy context. Many factors account for poor medication adherence, ranging from patient socioeconomic status to provider training. Accurately reporting which factors are being intervened upon, at what stage the factors are targeted using the ABC taxonomy (6), and taking into consideration the intervention components put forward by Michie et al. (25) are all necessary to ensure successful implementation that improves adherence.

Third, many behavioral interventions to improve medication adherence continue to lack adequate methodological rigor. The most recent Cochrane Library Review on medication adherence interventions (18) highlighted many issues with the methodological quality of medication adherence research; of the 182 papers included in the review, only 11 studies had the lowest risk of bias. This low quality of research on medication adherence and potential interventions hinders progress in the field.

The state of the science of adherence intervention research is primarily based on clinical trials designed to provide information on the efficacy of adherence interventions (e.g., better implementation or persistence). However, it cannot be assumed that efficacious interventions will automatically be implemented and prove equally effective in clinical practice. There are several

Dissemination: the process of spreading knowledge, information, or interventions to other settings

challenges to the implementation of adherence interventions, such as identifying evidence-based, effective interventions that are appropriate and feasible for implementation in various contexts. It is important but also challenging to identify interventions that were conducted with resources available in a clinical practice setting with real-world patients (e.g., complex comorbid conditions with polypharmacy) (26). Too often, issues surrounding the cost to implement, the time involved to administer an intervention, its scalability, sustainability, and fidelity are not adequately considered, which contributes to the lack of translation of scientific evidence into practice settings and leads to significant waste in research funding. Reports indicate that only one-third of evidence from such research projects is ever implemented in clinical practice, and, on average, it takes about 17 years for implementation to occur (27–29).

STUDY OBJECTIVES

As outlined above, medication nonadherence is a major public health issue that needs to be targeted effectively in real-world settings. There are gaps in the translation of evidence coming from effective medication adherence intervention trials that could be addressed by applying implementation science principles, which would result in sustainable solutions. We highlight areas that are important for investigators in the field of medication adherence research to consider in order to move effective interventions from the research setting (i.e., clinical trial and health services research world) into clinical care (i.e., the real world). In reviewing existing scholarly evidence our objectives are the following:

1. To showcase the information available in high-quality behavioral intervention studies that may be successfully translated into daily clinical practice.
2. To suggest approaches to medication adherence researchers, clinicians, policy makers, pharmaceutical companies, and other providers of care to show them how they can adopt the implementation science paradigm in their adherence (research) programs.
3. To explain a new research paradigm of implementation science and the necessity of creating a connection between the research setting and the context of the real world. This objective is accomplished by providing a best-practice example of a medication adherence study that can guide future researchers and clinicians in tackling medication nonadherence.

INFORMATION FOR IMPLEMENTATION IN HIGH-QUALITY TRIALS

To address the first objective, we analyzed high-quality papers (30–52, 83, 84) from recent Cochrane Library reviews (18, 54–60) addressing medication adherence with the goal of identifying potential programs ready for use moving from the trial (e.g., safety and efficacy) to the real world (e.g., dissemination and implementation).

Paper Selection and Data Extraction

Our objective was to identify high-quality articles addressing behavioral interventions that promote and support long-term medication adherence among adult patients. To identify relevant articles, we used a three-phase review process. First, we identified recently published Cochrane Database reviews. Second, we assessed the studies referenced in the included reviews for their risk of bias. Third, we extracted data from the included studies regarding study characteristics (Table 1) and reported implementation research components (Table 2). We describe each phase in detail below.

Table 1 Description of identified medication adherence intervention studies

| Study | Country, setting | Population | Sample sizes | Intervention | Control | Adherence phase; measurement | Adherence outcome | Clinical outcome |
|---|--|--|---------------------------------------|---|--------------------------------|---|--|---|
| Brown et al. (30) | United Kingdom; one outpatient neurology clinic, five MDs | Patients ≥ 16 years old with history of epilepsy taking antiepileptic drugs once or twice daily | $N = 69$ IG: 37 CG: 32 | Implementation intention intervention delivered through self-administered implementation worksheet (patients write down when and where they will take medication) | Usual care | Implementation/persistence, not differentiated; electronic monitoring | Percent of doses taken IG 93.4% versus CG 79.1%, $p < 0.01$ Percent of days correct doses taken IG 88.7% versus CG 65.3%, $p < 0.001$ Percent of doses taken on schedule IG 78.8% versus CG 53.3%, $p < 0.01$ Overall adherence IG 0.35% versus CG -0.40%, $p < 0.01$ | Not reported |
| Choudhry et al. (31) and methods paper (83) | United States; Aetna Health Insurance, 2,980 plan sponsors | Patients ≤ 65 years old discharged after myocardial infarction | $N = 5,855$ IG: 2,845 CG: 3,010 | Elimination of copayment for drugs | Usual care (i.e., co-payments) | Implementation/persistence, not differentiated; prescription refills | Absolute adherence IG 43.9% versus 38.9%, $p < 0.001$ Full adherence IG 12.1% versus 8.9%, $p < 0.001$ Subgroup analyses for ACE/ARB, beta-blocker, and statins significantly better in IG | Fatal or nonfatal vascular event: NS; total major vascular events and revascularization: IG 21.5 versus CG 23.3, $p = 0.03$; total spending cost: NS; patient costs, reduced for drugs and other services, $p = 0.001$ |

(Continued)

Table 1 (Continued)

| Study | Country, setting | Population | Sample sizes | Intervention | Control | Adherence phase; measurement | Adherence outcome | Clinical outcome |
|---------------------|--|---|---------------------------------------|---|-------------|---|--|---|
| Deroose et al. (32) | United States; 14 medical centers and 197 medical offices of Kaiser Permanente Southern California | Adults ≥ 24 years old with no history of statin use who did not fill a statin prescription after 1–2 weeks | $N = 5,216$ IG: 2,606 CG: 2,610 | Automated phone calls followed 1 week later by letters for continued nonadherence; education and prompt for outreach intervention | No outreach | Initiation; prescription refills | Medication adherence (initiation phase) IG 42.3% versus CG 26.0%, $p < 0.001$ RR for nonadherence in IG versus CG 0.78 (95% CI, 0.75–0.81) Difference persisted until 1-year follow-up, $p < 0.001$ | Not reported |
| Eussen et al. (33) | Netherlands; 26 community pharmacies | New users of statin therapy ≥ 18 years old | $N = 899$ IG: 439 CG: 460 | Five individual counseling sessions by pharmacist over 1 year; education and feedback on clinical outcome (lipids), drug information letter | Usual care | Implementation/persistence, not differentiated; prescription refills | Discontinuation rate at 6 months IG 11% versus CG 16%, $p = 0.026$ Discontinuation rate at 12 months IG 23% versus CG 26%, $p = 0.021$ | Significant decline of lipid levels |
| Farooq et al. (34) | Pakistan; one tertiary care mental health center | Adults 17–60 years old with schizophrenia or schizoaffective disorders | $N = 95$ IG: 49 CG: 46 | Free medication; directly observed therapy via trained family member living with the individual | Usual care | Implementation/persistence, not differentiated; self-report by patient and collateral report by family member | Complete adherence at 3 months IG 69.1% versus CG 50.9%, $p = 0.05$ Complete adherence at 6 months IG 72.7% versus CG 61.8%, $p = 0.23$ Complete adherence at 12 months IG 67.3% versus CG 45.5%, $p < 0.02$ | Significant improvement in symptoms and functioning |

(Continued)

Table 1 (Continued)

| Study | Country, setting | Population | Sample sizes | Intervention | Control | Adherence phase; measurement | Adherence outcome | Clinical outcome |
|---------------------|---|--|---|---|--|--|--|--|
| Fisher et al. (35) | United States; five large HIV clinics | HIV+ adults ≥18 years old on ARV therapy | N = 564 (ITT) IG: 277 CG: 287 N = 328 (OP) IG: 152 CG: 176 | LifeWindows: interactive computer-based ARV adherence promotion (average time 26 min); tailored adherence intervention based on barriers assessment and patient preferences for specific adherence strategy (e.g., strategy selection, intervention activity, goal selection) | Introduction of LifeWindows and general assessment, but no intervention components (average time 14 min) | Implementation/persistence, not differentiated; self-report | ITT: no significant effects OP: significant main effect of study arm assignment on perfect 3-day ARV adherence, $p = 0.024$; effect retained down to 70% adherence cutoff | Proportion with nondetectable viral load higher in IG (79%) than CG (74%) but NS over time |
| Goswami et al. (36) | United States; one single-specialty cardiovascular physician practicing with ten practicing cardiologists | Adults >21 years old prescribed atorvastatin | N = 208 IG: 155 CG: 53 | 5–10 min adherence counseling from nurse and adherence tip sheet; optional: 12-week guide to manage cholesterol (educational intervention); copy relief card decided by MD, monthly newsletter | Usual care | Implementation/persistence, not differentiated; prescription refills | Proportion of days covered, adherence ≥80% over 6 months IG 71.6% versus CG 71.7%, $p = 0.95$ Medication possession ratio, adherence ≥80% over 6 months IG 76.8% versus CG 75.5%, $p = 0.75$ Persistence over 6 months IG 146.3 ± 54.1 versus CG 147.4 ± 52.6, $p = 0.55$ | Not reported |

(Continued)

Table 1 (Continued)

| Study | Country, setting | Population | Sample sizes | Intervention | Control | Adherence phase; measurement | Adherence outcome | Clinical outcome |
|--------------------|---|--|--------------------------------------|---|---------------------------------------|---|---|---|
| Gray et al. (37) | United Kingdom; Manchester Royal Eye Hospital clinics | Newly diagnosed patients with open-angle glaucoma or hypertension on eye drop treatment | <i>N</i> = 127 IG: 64 CG: 63 | Individual assessment of health care needs and beliefs, training in eye drop treatment by a glaucoma expert nurse, and a 1-year follow-up (tailored intervention based on assessment) | Usual care | Implementation/persistence, not differentiated; prescription refills; self-report | 100% refill adherence IG 70% versus CG 43%, <i>p</i> = 0.002 More prescriptions in IG, <i>p</i> < 0.001 IG better adherence than CG, <i>p</i> < 0.001 | Change in mean intraocular pressure NS at 12 months; change in intraocular pressure fluctuation NS at 12 months |
| Ho et al. (38) | United States; four VA medical centers | Patients admitted with acute coronary syndrome using VA medical center for their usual care on cardioprotective medication | <i>N</i> = 241 IG: 122 CG: 119 | Pharmacist-led medication reconciliation and tailoring, patient education, collaborative care between pharmacist and PCP, and voice messaging for educational purpose and refill reminder | Usual care | Implementation/persistence, not differentiated; prescription refills | Adherence IG 89.3% versus CG 73.9%, <i>p</i> = 0.003 Mean proportion of days covered IG 0.94 versus CG 0.87, <i>p</i> < 0.001 | Blood pressure control, change in LDL cholesterol level, readmission for myocardial infarction revascularization, death; NS; NS cost outcomes |
| Janson et al. (39) | United States; private and public community clinics in San Francisco area | Adults with moderate to severe asthma | <i>N</i> = 84 IG: 45 CG: 39 | Individualized self-management educational 30-min interventions including self-monitoring of symptoms and peak flow | Usual care with self-monitoring alone | Implementation/persistence, not differentiated; electronic monitoring | Higher adherence levels and ninefold greater odds of >60% adherence to prescribed dose at end of intervention, <i>p</i> = 0.02 Maintained threefold greater odds of >60% adherence at end of study | Improved perceived control of asthma (<i>p</i> = 0.006), decreased nighttime awakenings (<i>p</i> = 0.03), and decreased inhaled β-agonist use (<i>p</i> = 0.01) |

(Continued)

Table 1 (Continued)

| Study | Country, setting | Population | Sample sizes | Intervention | Control | Adherence phase; measurement | Adherence outcome | Clinical outcome |
|---|-----------------------------------|--|-------------------------------|---|---|--|---|--|
| Lai et al. (40) | Malaysia; academic medical center | Postmenopausal osteoporotic women initiating once weekly alendronate or risedronate | N = 198 IG: 100 CG: 98 | Counseling on osteoporosis, risk factors, lifestyle modifications, goals of therapy, side effects, and the importance of adherence | Usual care | Persistence; self-report of pill count | IG reported higher medication adherence at 6 months ($p = 0.015$) and 12 months ($p = 0.047$) | No difference in bone turnover markers serum CTX-I and serum OC reduction at 3 and 6 months |
| Lester et al. (42) and methods paper (41) | Kenya; three HIV clinics | HIV+ adults starting ARV therapy | N = 538 IG: 273 CG: 265 | Weekly mobile phone SMS intervention from clinical nurse requiring response within 48 h; nurse contacted patient by phone in case of no response or issue | Usual care: 1–2 counseling sessions at start of ARV | Implementation/persistence, not differentiated; self-report | Adherence >95% IG 62% versus CG 50%, $p = 0.006$ (ITT) | Viral load decrease IG 57% versus CG 48%, $p = 0.04$ |
| Marquez Contreras et al. (43) | Spain; five primary care centers | Patients 18–80 years old with hypercholesterolaemia | N = 188 IG: 96 CG: 92 | Calendar reminder of medication taking (front side), dates of next visit, recommendations, and a space to note blood pressure (back side) | Usual care | Implementation/persistence, not differentiated; electronic monitoring | Percent of doses taken IG 92% versus CG 84%, $p < 0.05$ % of days with correct dose taken IG 86% versus CG 81%, $p < 0.05$ | Decline in lipids significantly higher in IG |
| Mehuys et al. (44) | Belgium; 66 community pharmacies | Patients with type 2 diabetes who regularly visit the pharmacy and are on treatment with oral hypoglycemic medication for min. 12 months | N = 288 IG: 153 CG: 135 | Pharmacist intervention focused on correct medication use, adherence, and healthy lifestyle promotion | Usual care | Implementation/persistence, not differentiated; prescription refills and self-report | No noteworthy differences between groups | Initial lower HbA1c in IG (between-group difference 0.5%, $p = 0.009$); NS difference between groups 18 months after study period |

(Continued)

Table 1 (Continued)

| Study | Country; setting | Population | Sample sizes | Intervention | Control | Adherence phase; measurement | Adherence outcome | Clinical outcome |
|--------------------------|--|---|---|--|---|---|--|---|
| Mullan et al. (45) | United States; 11 primary care and family medicine sites in Mayo Clinic Health System, and Olmsted Medical Center | Physicians and midlevel providers managing diabetes; adult patients with type 2 diabetes mellitus for ≥ 1 year | $N = 40$ clinicians and 85 patients IG: 21 clinicians and 48 patients CG: 19 clinicians and 37 patients | Decision aid tool to enable discussions about advantages and disadvantages of adding an agent | Usual care | Persistence; prescription refills and self-report | Nearly perfect medication use in both groups (median, 100% of days covered) at 6 months with better adherence (AMD, 9% more days covered; 95% CI, 4–14%) and persistence (AMD, 12 more days covered; 95% CI, 3–21 days) than in the CG | No significant impact on HbA1c levels (AMD, 0.01; 95% CI, –0.49 to 0.50) |
| Murray et al. (46) | United States; four general medicine practices, one cardiology practice, and one inner-city university-affiliated hospital | Adults ≥ 50 years old with heart failure | $N = 314$ IG: 122 CG: 192 | Pharmacist-delivered intervention: baseline medication history, results of an assessment of patient medication knowledge and skills, and dispensing 2 months of medication | Usual care | Implementation; prescription refills and electronic monitoring | Medication adherence during intervention IG 78.8% versus CG 67.9% (95% CI, 5.0–16.7%) Medication adherence at 3 months IG 70.6% versus CG 66.7% (95% CI, 5.9–6.5%) | 19.4% fewer ER visits and hospital admissions [incidence rate ratio, 0.82 (CI, 0.73–0.93)]; annual direct health care costs lower [–\$–2,960 (CI, \$–7,603 to \$1,338)] in IG |
| Ogedegbe et al. (47, 48) | United States; primary care practices affiliated with New York Presbyterian Hospital | English-speaking African Americans with hypertension | $N = 256$ IG: 125 CG: 131 | Culturally tailored hypertension self-management workbook, behavioral contract, bimonthly phone calls to overcome medication adherence barriers and foster self-affirmation, small gifts | Hypertension self-management workbook, behavioral contract, and bimonthly phone calls | Implementation (12 months); electronic monitoring and self-report | Medication adherence at 12 months IG 42% versus CG 36%, $p = 0.049$ | NS differences between groups in blood pressure improvement |

(Continued)

Table 1 (Continued)

| Study | Country, setting | Population | Sample sizes | Intervention | Control | Adherence phase; measurement | Adherence outcome | Clinical outcome |
|--|--|--|--|--|---------------------------------------|--|--|---|
| Simoni et al. (84) | United States; public HIV specialty clinic in Seattle | HIV+ patients initiating or changing ≥ 2 medications of a HAART regimen | $N = 226$ IG1: 56 IG2: 57 IG3: 56 CG: 57 | IG1: peer support IG2: pager messaging IG3: peer support and messaging | Usual care | Implementation (9 months); electronic monitoring and self-report | Peer intervention associated with greater adherence; pager intervention not significant | No difference in clinical biomarkers |
| Solomon et al. (50) and methods paper (49) | United States; pharmacy benefits program beneficiaries | Patients initiating osteoporosis medication | $N = 2,097$ IG: 1,050 CG: 1,047 | 10 one-on-one telephone-based motivational interviews, counseling intervention, and mailed education | 12-month mailed educational materials | Implementation/persistence, not differentiated; prescription refills | Median adherence IG 49% versus CG 41%, $p = 0.074$ | No differences in fractures |
| Staring et al. (51) | Netherlands; not specified | Patients with schizophrenia or schizoaffective disorder receiving outpatient treatment | $N = 109$ IG: 54 CG: 55 | Psychiatric nurse-delivered motivational interview, tailoring/optimization of medications, and behavioral training | Usual care | Implementation; self-report | Treatment adherence therapy significantly benefited medication adherence versus control care (Cohen's $d = 0.43$) | No impact on symptoms or quality of life |
| Taiwo et al. (52) | Nigeria; antiretroviral clinic | HIV-1-infected treatment-naïve adults | $N = 499$ IG: 248 CG: 251 | Treatment partners attended one adherence education session and observed participants taking HIV drugs min. 1 per day, assisted with reporting and management of adverse effects, and reminded participants of drug pickup | Usual care | Initiation/discontinuation; observation of prescription pickup | TPA group had more than three times the odds of at least 95% drug pickup adherence through week 24 (OR = 3.06; 95% CI, 1.89–4.94; $p = 0.01$) and almost two times the odds through week 48 (OR = 1.95; 95% CI, 1.29–2.93; $p = 0.01$) | Undetectable viral load IG 61.7% versus CG 50.2% (OR = 1.58; 95% CI, 1.11–2.26, $p = 0.05$) |

Abbreviations: ARV, antiretroviral; CG, control group; CI, confidence interval; IG, intervention group; ITT, intention-to-treat; NS, nonsignificant; OP, on protocol; OR, odds ratio; PP, per protocol; RR, relative risk; TPA, treatment partner–assisted therapy; VA, Veterans Affairs; VAS, visual analog scale.

Table 2 Description of implementation research components reported in the included studies

| | Study | | | | | | | | | | | | | | | | | | | | | |
|---|-------|-----------|----|----|----|----|----|----|----|----|----|----|----|----|----|-----------|----|----|----|----|----|--|
| | 30 | 31, 83 | 32 | 33 | 34 | 35 | 36 | 37 | 38 | 39 | 40 | 42 | 43 | 45 | 46 | 47, 48 | 84 | 50 | 51 | 52 | 80 | |
| Did the investigators describe the health care and organizational context? | | | | | | | | | | | | | | | | | | | | | | |
| Did the investigators describe the social, economic, and policy context? | | | | | | | | | | | | | | | | | | | | | | |
| Were patient and/or family members involved in designing or evaluating the study? | | | | | | | | | | | | | | | | | | | | | | |
| Were other stakeholders, besides patients, involved in designing or evaluating the study? | | | | | | | | | | | | | | | | | | | | | | |
| Was the included sample representative for the studied population? | | | | | | | | | | | | | | | | | | | | | | |
| Was the research conducted in a real-world setting? | | | | | | | | | | | | | | | | | | | | | | |
| Was a feasibility or pilot study conducted before the evaluation study? | | | | | | | | | | | | | | | | | | | | | | |
| Was an implementation strategy reported? (63, 64) | | | | | | | | | | | | | | | | | | | | | | |
| Was a process evaluation conducted parallel to the outcome evaluation? | | | | | | | | | | | | | | | | | | | | | | |
| Were implementation outcomes such as adoption and costs measured? (65) | | | | | | | | | | | | | | | | | | | | | | |

Table evaluates implementation studies on whether authors clearly addressed an implementation component (green), mentioned but did not thoroughly address a component (orange), or failed to address a component (red). Reference 80 was not part of the review process but is an example of a medication study embracing the research paradigm of implementation science. Table adapted from Peters et al. (62).

Phase 1. We searched MEDLINE via PubMed for Cochrane Database systematic reviews that were published from January 1, 2014, through November 9, 2017, addressing medication adherence. The following was our search strategy:

```
((("2014/01/01"[Date - Publication]: "3000"[Date - Publication])) AND Cochrane Database Syst Rev.) AND (((((((("Medication Adherence"[Mesh]) OR ("Patient Compliance"[Mesh:noexp]) OR (adherence[tiab] OR adherent[tiab]) OR (compliance[tiab] OR compliant[tiab]) OR (nonadherence[tiab] OR nonadherent[tiab]) OR (nonadherence[tiab] OR nonadherent[tiab]) OR (noncompliance[tiab] OR noncompliant[tiab]) OR (noncompliance[tiab] OR noncompliant[tiab]) OR ("Patient Dropouts"[Mesh]) OR ("Treatment Refusal"[Mesh]) OR (treatment refusal[tiab]))) OR (treatment refusals[tiab])) OR (treatment refusing[tiab])) OR (missed dose*[tiab])))
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Three reviewers (L.L.Z., M.D., and S.D.G.) independently assessed the titles and abstracts of identified Cochrane Database reviews for relevance to (a) medication adherence, (b) long-term or chronic medication use, and (c) adult populations. The reviewers then met and discussed differences in their categorization.

Phase 2. Two reviewers (L.L.Z. and M.D.) independently assessed all individual studies published after 2005 that had a low risk of bias using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (61). We included papers that had (a) no criteria evaluated as a high risk of bias and (b) a maximum of five criteria evaluated as an unclear risk of bias, or one criterion evaluated as high risk of bias in combination with up to four criteria evaluated as an unclear risk of bias. The data for assessing risk of bias were captured from the included Cochrane review analyses. When there were discrepancies in the review, decisions regarding study eligibility were made in discussion with a third reviewer (S.D.G.) who acted as an arbitrator.

Phase 3. Two teams of reviewers (L.L.Z. and H.B.B.; M.D. and S.D.G.) read the full text to extract data from the included studies. The teams extracted data on country, population, setting, sample size, intervention, control, adherence phase, adherence measurement, adherence outcome, and clinical outcome from each study (**Table 1**). Next we evaluated components of the included papers that are of potential relevance for implementation derived and adapted from a seminal paper on implementation research (62). These factors include the following:

1. information about the health care and organizational context;
2. the social, economic, and policy context;
3. patient/family and other stakeholder involvement;
4. the representativeness of the sample for the studied population;
5. whether the work was conducted in a real-world setting;
6. whether a feasibility study preceded the evaluation study;
7. whether the research describes an implementation strategy (63, 64);
8. whether a process evaluation was conducted parallel to the outcome evaluation; and
9. whether implementation outcomes were included (65).

We applied a qualitative approach to extracting this information. The reviewer teams assigned each intervention component with a three-tier, color-coded scale (i.e., green, orange, red) shown in **Table 2** regarding whether the authors clearly addressed an implementation component (e.g., the health care context was extremely well defined and measured), the authors mentioned but did not thoroughly address a component or whether it was uncertain, and whether the authors did not address a component at all.

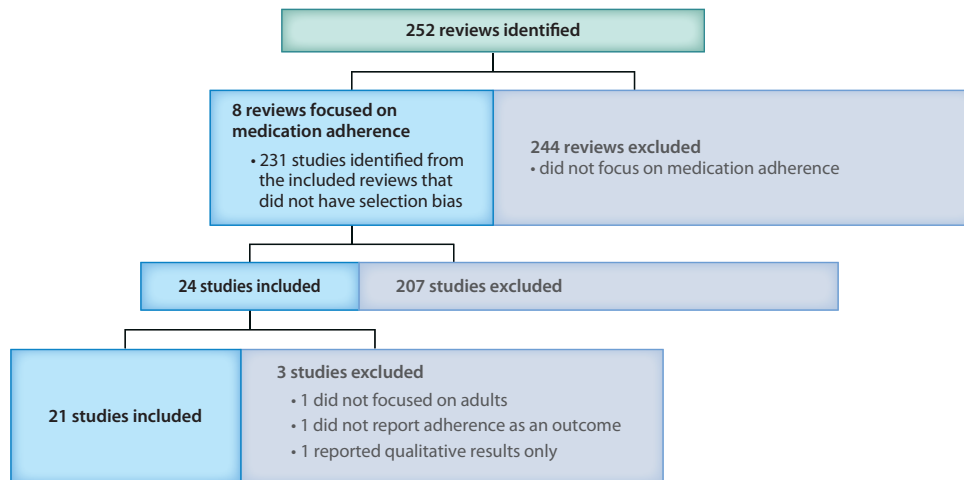


Figure 2
Flowchart of literature search.

Description of the Included Papers

The initial search in the Cochrane Review Library yielded 252 reviews of which 8 reported on medication adherence (18, 54–60). These 8 reviews covered 231 original studies that did not have selection bias. At the second review phase, we retained a total of 24 studies. During the full review, 3 additional articles were excluded (one did not focus on adults, one did not report adherence as an outcome, and one reported qualitative results only), resulting in a final number of 21 included articles (**Figure 2** and **Table 2**).

Eleven studies were conducted in the United States, six in Europe, one in Malaysia, and three in lower-middle-income countries as determined by the 2017 World Bank list. Sample sizes range between 69 and 5,855 patients with a total of 18,486 patients included in all studies. Studied populations include patients with hypercholesterolemia ($n = 4$), HIV ($n = 4$), cardiac problems ($n = 3$), schizophrenia ($n = 2$), osteoporosis ($n = 2$), diabetes ($n = 2$), epilepsy ($n = 1$), glaucoma ($n = 1$), asthma ($n = 1$), and hypertension ($n = 1$). Regarding the phases of medication adherence, two studies focused the intervention on medication initiation, two focused on persistence, and four focused on implementation, while in 13 studies no differentiation was or could be made between the implementation and persistence phases. Medication adherence was measured using prescription refill data ($n = 7$), self-reporting ($n = 5$), electronic monitoring ($n = 3$), or a combination of two of these measures ($n = 6$). Sixteen studies (76%) reported statistically significant differences on at least one of the reported medication adherence outcomes. Of the 18 studies reporting on clinical outcomes, 10 studies (56%) reported statistically significant outcomes.

Description of Implementation Research Components

Very few studies described the components of implementation research in detail (**Table 2**). Health care and organizational context and social, economic, and political context were well-articulated in two studies, respectively (42, 52). Only two studies reported engaging stakeholders in some phase of their research efforts (34, 42); one reported conducting feasibility work prior to the study (34), and one conducted a process evaluation in parallel with the primary study to inform potential

future implementation efforts (42). Furthermore, only two studies reported that the study sample was adequately representative of the underlying population being studied (31, 32). Five studies were conducted in real-world settings (31, 32, 42, 44, 50), or settings that were comparable to actual clinical practice rather than artificial research settings.

Across all implementation research components, the majority of studies either did not address a component altogether or did not address them in sufficient detail for the review to interpret a component (**Table 2**). Finally, none of the included studies clearly defined an implementation strategy or implementation outcome.

HOW TO ADOPT THE IMPLEMENTATION SCIENCE PARADIGM IN ADHERENCE (RESEARCH) PROGRAMS

Beyond the few adherence interventions that have demonstrated improvements in both medication adherence and biological outcomes (18), few of these programs have been implemented, scaled, and sustained in a health care setting. Given the public health significance of inadequate medication adherence, greater global investment is needed for rigorous adherence research that strengthens the evidence base of adherence related science. There is also a need to focus on conducting research with the end in mind. In other words, we must ensure that adherence interventions are developed and evaluated such that they can be scaled and applied in clinical practice (real-world settings).

It appears that investigators involved in studying adherence interventions lack a full appreciation of implementation science. Implementation science is defined as the study of methods to promote the integration of research findings and evidence into health care policy and practice. Typically, implementation science applies interventions that have already been proven safe and effective in a research setting. Curran et al. (66) showcase different implementation science study designs and hybrid approaches to marry clinical research and implementation methodology. Implementation science requires embracing complexity by involving stakeholders from the start through all phases of the project. Successful implementation involves performing a thorough contextual analysis (i.e., on individuals and the inner and outer settings) (67) with ample attention to factors that are relevant for the development, implementation, and scaling up of the intervention. It may also require the assessment of factors that might hinder or facilitate implementation of the intervention to translate the clinical trial efficacy results into effective and sustainable real-world interventions.

Development and evaluation of implementation strategies are inherent parts of this approach. Integration of implementation science approaches is critical to streamline the process for getting key evidence when and where it is most needed: for patient care carried out in clinical practice leading to optimal health outcomes and quality of life, while maintaining a realistic awareness of resources and economic outcomes.

Even before or during the conduct of an efficacy study, there is a need to consider implementation science principles. Implementation science considerations for efficacy and effectiveness (phase 1–3) trials include the following:

1. need to acknowledge and engage potential stakeholders,
2. appropriate selection of interventions components that have the potential to be considered for further implementation,
3. consideration of evaluation and future adaptation, and
4. appropriate and rigorous evaluation.

These principles exist to identify potential stakeholders in the development, implementation, and evaluation of the program. Potential stakeholders within the five P's (i.e., patient, provider, payer, pharma, policy maker) should not be expected to implement a program if they do not

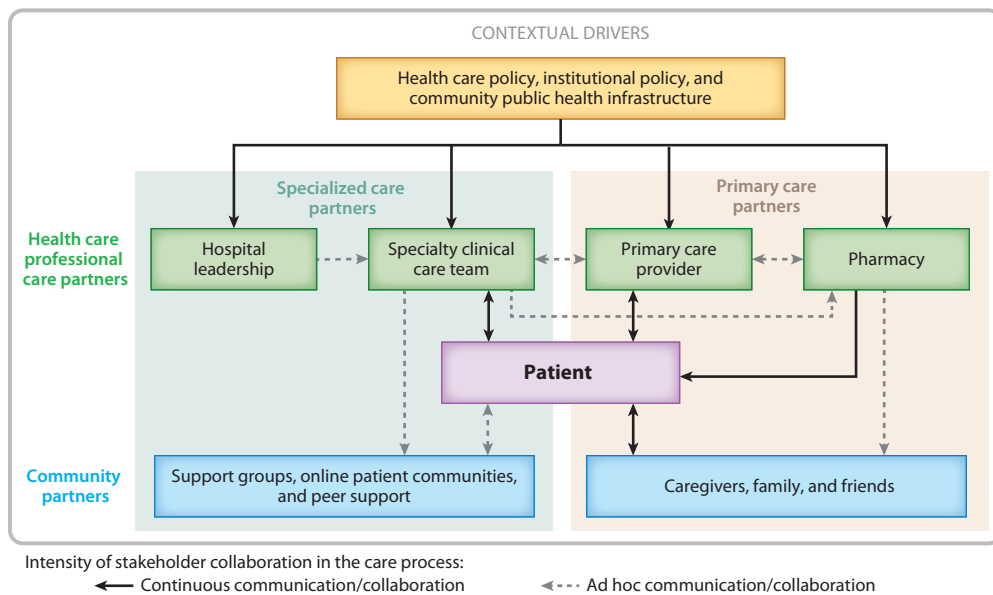


Figure 3

Illustration of the contextual drivers associated with adherence. These drivers are related factors that should be considered when implementing adherence interventions.

perceive the value and evaluation mechanisms of the program (68). Important considerations include identifying the appropriate level or levels of stakeholders, the appropriate representatives of these stakeholders, the frequency of contact, and the sharing and eliciting of information. The key factors for successful implementation are the nature of the topics chosen for improvement; the capacity and motivation of participating teams, particularly their leadership and team dynamics; and the motivation and receptivity to change of the organizations they represent (**Figure 3**) (69).

Identification of critical interventions and/or components to be considered for further dissemination/implementation is important. Time, cost, and resources must be evaluated to ensure appropriate identification for further scalability and dissemination, yet these data are rarely collected. In addition, Everett Rogers' textbook *Diffusion of Innovations* provides a helpful model to identify additional appropriate interventions worthy of further implementation (70). Rogers asserted that there are five general characteristics of innovations that influence an organization's or an individual's decision to adopt or reject that innovation: relative advantage, compatibility, complexity or simplicity, trialability, and observability. Relative advantage indicates the degree of improvement an innovation brings over the previous generation. The level of compatibility embraces the idea that an innovation must be assimilated into an individual's life or an organization's culture and fit well with it. Complexity expresses the idea that if people or organizations think the innovation is complicated or difficult to use, they are unlikely to use it. Trialability addresses how easily an innovation can be experimented with. If an organization can try out the intervention on a small scale and see how it works, then they may be more likely to adopt it in the long run. Finally, observability addresses the extent to which the innovation is visible to others (70).

In addition to engaging stakeholders and identifying which interventions should be considered for implementation, and when, there is the challenge of balancing the fidelity and adaptability of the intervention. It is important to consider the degree to which an intervention can be adapted,

tailored, refined, or reinvented to meet local needs in order to ensure adequate implementation. Adaptability relies on a definition of the core components (the essential and indispensable elements of the intervention itself) versus the adaptable periphery (adaptable elements, structures, and systems related to the intervention and organization into which it is being implemented) of the intervention (69, 71). A component analysis can be performed to identify the core versus adaptable periphery components (72), but often the distinction is one that can only be discerned through trial and error over time as the intervention is disseminated more widely and adapted for a variety of contexts (73). The tension between the need to achieve full and consistent implementation across multiple contexts while providing the flexibility for local sites to adapt the intervention as needed is real and must be balanced, which is no small challenge (74, 75).

Appropriate and Rigorous Evaluation

In practice, given the nature of the physical locations where medication adherence interventions occur, evaluations of interventions often take place in a wide range of settings that may constrain researchers' choice of evaluation methods. Researchers need to carefully consider the trade-off between the importance of the intervention and the value of the evidence that can be gathered given financial and study constraints. Although experimental methods are often considered the gold standard, there may be political or ethical objections to using them to assess adherence interventions in some cases. Given the potential cost of such interventions, evaluation should still be considered—the best available methods, even if they are not optimal in terms of internal validity, may yield useful results (76).

If nonexperimental methods are used, researchers should be aware of their limitations and interpret and present the findings with due caution. Researchers should be prepared to explain to decision makers the need for adequate development work, the pros and cons of experimental and nonexperimental approaches, and the trade-offs involved in settling for less reliable methods. Researchers should also be prepared to challenge decision makers when interventions of uncertain effectiveness are being implemented in a way that would make strengthening the evidence through a rigorous evaluation difficult, or when a modification of the implementation strategy would open the possibility of a much more informative evaluation (77).

Process evaluations, which explore the way the intervention being studied is implemented, can provide valuable insights on why an intervention fails or has unexpected consequences and why a successful intervention works and how it can be optimized. A process evaluation nested inside a trial can be used to assess the fidelity and quality of implementation, to clarify causal mechanisms, and to identify contextual factors associated with variation in outcomes (78). However, process evaluation is not a substitute for an evaluation of outcomes.

Variability in implementation, preplanned or otherwise, makes it important that both process and outcome evaluations are reported fully and that a clear description of the intervention is provided to enable replication and synthesis of evidence (79). The key message for stakeholders is the need to consider evaluation requirements in the planning of new initiatives and, wherever possible, to allow for an experimental or high-quality nonexperimental approach to the evaluation of initiatives when there is uncertainty about their effectiveness.

EXAMPLE OF A MEDICATION ADHERENCE STUDY EMBRACING THE BEST-PRACTICE RESEARCH PARADIGM OF IMPLEMENTATION SCIENCE

Although we uncovered several quality medication adherence-improving studies with a low risk of bias (**Table 1**), relatively few addressed most of the elements that are relevant for implementation

science (**Table 2**) and thus did not provide a solid basis to move the evidence quickly from the trial to the real world. Even among those that did address some elements, none of the studies addressed most of the components set forth by Peters et al. (62) (**Table 2**). To illustrate how implementation science can be used to strengthen adherence research to facilitate and accelerate future implementation of the evidence (i.e., from the trial to the real world), we provide a case study from our own work.

Bosworth and colleagues (80) conducted a tailored, telephone-based behavioral self-management intervention to improve medication adherence among patients with hypertension. The study was based on a prior effective intervention (81) and was also theoretically based (80). The intervention content addressed improving adherence to several recommendations for hypertensive patients including the Dietary Approaches to Stop Hypertension (DASH) diet, weight loss (for patients who were overweight), reduction in sodium intake, regular physical activity, alcohol consumption in moderation, and adherence in taking medications as prescribed. Patients were also given tools for home-based blood pressure self-monitoring.

The study had several design elements that made it ideal for implementation. The authors identified the core components of the intervention (e.g., those that must remain intact to ensure the intervention's effectiveness), which were educational and self-management modules addressing medication and side effects. They also identified ancillary modules that were important but not considered core (e.g., diet, hypertension knowledge, social support). These ancillary modules could potentially be modified or adapted if the study was implemented in a different setting or a different patient population. The project did not rely on research staff to deliver the intervention. Clinic staff engaged with their patients and delivered the intervention. Although these elements are not required for an implementation study, their presence suggests that the program is feasible for implementation with typical clinic resources and when local stakeholders are engaged and invested in the program.

The Bosworth et al. (80) study incorporated most of the key implementation science components listed in **Table 2**. More specifically, the authors clearly defined the health care and organizational context. The project was conducted among 14 community-based networks across the state of North Carolina in the United States. These networks are part of the Community Care of North Carolina (CCNC) program and are linked to primary care practices and patient-centered medical homes. In short, this is a well-described, real-world setting. The authors also describe the social, economic, and policy context of the intervention. They discuss the organization of CCNC and how it is integrated with health care payers including US Medicaid and Medicare, which provides a broad sense of external factors that might influence the program's delivery and outcomes. Although the authors did not explicitly discuss engaging patients and/or family members in their work, administrative and clinical stakeholder involvement was clearly central to the study design. The authors reported that "the three locations that implemented the program were the three most enthusiastic regarding the program. Before the program was implemented, the three sites identified hypertension as a problem in their organizations and were supportive of the program" (80, p. 194). This local buy in is evidence of stakeholder involvement and is critical for implementation success. The authors also used very broad eligibility criteria and recruited directly from community sites, which improved the representativeness of the sample for the studied population. Although the authors did not expressly conduct a feasibility study in the CCNC sites, they did base their work on a previous, well-described research study (81). The intervention used several different implementation strategies (82), including capturing and sharing local knowledge, centralizing technical assistance, developing educational materials, conducting ongoing training, informing opinion leaders, and working with educational institutions. There

was no process evaluation conducted in parallel with the main study, and process outcomes were not included.

Using a pharmacy-based measure of medication adherence (e.g., the medication possession ratio), the study showed a significant improvement in medication adherence (80). However, it failed to report clinical or implementation-specific outcome measures. In best practice, implementation-oriented adherence studies should report outcomes in several categories including adherence, clinical, and implementation measures.

CONCLUSION

Poor medication adherence is a common and multifaceted public health problem. Many interventions to improve adherence have been tested without consideration of elements that facilitate implementation of the trial interventions to the real world (i.e., reach, resources, or cost) (29). We assert that future behavioral interventions must be designed practically with specific attention given to applicability, scalability, and sustainability in clinical settings. Many existing high-quality medication adherence studies were not designed with sufficient attention to future implementation. Similarly, most of the studies that we identified did not report their findings in sufficient detail to potentially inform future implementation.

We assert that future studies seeking to bridge the fields of medication adherence and implementation science could use the questions posed in **Table 2** as a checklist, both for thoughtful study design and as an approach to ensure reporting of information that is relevant to implementation. By ensuring that key implementation questions are addressed, the potential for implementing successful interventions into clinical practice may increase, thereby helping the field reach its ultimate goal of improving patients' medication adherence, associated clinical outcomes, and quality of life.

SUMMARY POINTS

1. Integrating implementation science approaches is critical to streamline the process for getting key evidence when and where it is most needed: in patient care for optimal health outcomes and quality of care.
2. To ensure that medication adherence is improved on the population level, it is important to plan for future potential implementation when designing and conducting studies.

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