

Systematic review of the impact of medication synchronization on healthcare utilization, economic, clinical, and humanistic outcomes

Prajakta H. Waghmare Ph.D.¹  | Rachel Lindsey Pharm.D.¹ | Jason B. Reed M.S.² |
 Sujuan Gao Ph.D.³ | Alan J. Zillich Pharm.D., FCCP⁴ 

¹Department of Pharmacy Practice, Purdue University College of Pharmacy, West Lafayette, Indiana, USA

²Purdue University, Libraries and School of Information Studies, West Lafayette, Indiana, USA

³Department of Biostatistics & Health Data Science, Indiana University School of Medicine, Indianapolis, Indiana, USA

⁴Department of Pharmacy Practice, Purdue University College of Pharmacy, Indianapolis, Indiana, USA

Correspondence

Alan J. Zillich, Pharm.D., FCCP, Department of Pharmacy Practice, Purdue University College of Pharmacy, 640 Eskenazi Ave, Indianapolis, IN 46202, USA.

Email: azillich@purdue.edu

Funding information

Community Pharmacy Foundation, Grant/Award Number: Grant Number 170; Purdue University College of Pharmacy Department of Pharmacy Practice

Abstract

Medication synchronization (med-sync) or appointment-based medication synchronization (ABMS) programs allow patients to have their chronic medication refills aligned to one pickup day. For patients on multiple chronic medications, it provides a more manageable way of picking up those medications. The objective of the study was to systematically characterize literature describing economic and healthcare utilization, clinical, and humanistic outcomes for patients enrolled in med-sync. A literature search was conducted on PubMed, International Pharmaceutical Abstracts (Ovid), CINAHL (EBSCO), EMBASE (Elsevier), and Cochrane Library. Studies were included if they were conducted at a pharmacy in the United States, between January 2008 and October 2022, and evaluated the impact of med-sync on at least one of the four outcomes of interest (utilization, economic, clinical, and humanistic). The title and abstracts were screened, followed by a full-text review and final data extraction by two researchers. A data extraction template and Cochrane risk of bias tool were used for data collection and quality assessments, respectively. The search resulted in 1617 studies and finally, 27 studies were included in the systematic review. All studies included patients enrolled in either ABMS, med-sync, or in conjunction with other pharmacy services. Across all studies evaluating medication adherence, proportion of days covered (PDC) increased. All studies that administered patient surveys showed a majority of patients were satisfied with their med-sync program. One study showed a reduction in healthcare utilization and costs, while another study indicated no change. Med-sync programs have shown clinical outcomes, specifically to improve adherence in patients taking chronic medications. In terms of humanistic outcomes, patient surveys have shown high rates of satisfaction with med-sync programs. Additional studies are needed to determine if med-sync can lead to improvements in healthcare utilization and cost outcomes.

KEYWORDS

adherence, healthcare utilization, medication synchronization, refill synchronization

This is an open access article under the terms of the [Creative Commons Attribution-NonCommercial-NoDerivs](https://creativecommons.org/licenses/by-nc-nd/4.0/) License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

© 2023 The Authors. JACCP: *Journal of the American College of Clinical Pharmacy* published by Wiley Periodicals LLC on behalf of Pharmacotherapy Publications, Inc.

1 | INTRODUCTION

Medication non-adherence may lead to adverse drug reactions and hospitalizations.^{1,2} Patient barriers include forgetting to take medications, concern about adverse effects, and access to medications.³ The solution to the quality, safety, and value challenges in the healthcare system is to understand and address the processes, and to take a systems approach to addressing them.⁴ A systems approach to health is one that applies, and alters design, processes, or policies based on the resultant knowledge in order to produce better health at lower cost. One of the strategies provided by the Institute for Safe Medication Practices for risk reduction related to medication adherence is to have refill reminder programs that automatically prioritize and refill prescriptions in a timely manner.⁵ Medication synchronization (med-sync) is one such program, which aligns patients' monthly or quarterly chronic medications to a predetermined single pickup date at a community pharmacy.⁶ Through reduced number of visits to the pharmacy, med-sync can improve access to medications by reducing time and transportation costs to patients as well as reduce disruption in medication treatment.⁷ Appointment-based model (ABM) med-sync programs can be implemented to enhance automatic syncing; wherein the med-sync program goes beyond automatic refills, and introduces supportive clinical services such as comprehensive and targeted medication reviews performed by the pharmacist.^{6,8} The initial steps take place during the first patient encounter and the recurring steps are performed every month (Figure 1).

The ABM med-sync program can mitigate certain patient barriers to taking medications as prescribed (e.g., missing doses, refilling the medication late, not refilling the medication, stock piling) and medication persistence (e.g., discontinuing medication before a recommended date), while also facilitating greater pharmacist oversight by addressing other medication therapy problems such as potential

contraindications, duplicate drug therapy, and errors.^{7,9,10} These programs also provide opportunities for counseling on targeted disease states and coordination of care for referrals to other providers. Barriers related to social determinants of health (e.g., affordability, living conditions, disability, transportation, and literacy) can also be identified and addressed more proactively as there is a regularly scheduled pharmacist-patient interaction.

The objective was to systematically characterize literature describing healthcare utilization, cost clinical, and humanistic outcomes for patients enrolled in med-sync.

2 | METHODS

The study protocol was registered and published on Preferred Reporting Items for Systematic Reviews and Meta-Analyses PROSPERO (CRD42021222618). Electronic search methods were adopted for identification of studies. A systematic literature search was conducted on PubMed, International Pharmaceutical Abstracts (Ovid), CINAHL (EBSCO), EMBASE (Elsevier), and Cochrane Library using the terms "medication synchronization," "refill synchronization," and other related terms (see Table A1 for full details). Search strategy was modified from a similar search created by Renfro et al., and additional terms were added.¹¹ These studies were imported on Covidence.¹² After removing duplicates, records were reviewed for inclusion in a two-step process. Step 1 was reviewing the titles and abstracts of all records. A pilot of the inclusion and exclusion criteria was performed by two reviewers on the first 100 results, with the remaining 1517 articles individually reviewed. Records were only eliminated at this stage if they clearly met one or more of the exclusion criteria (Table 1). If eligibility was uncertain, the record was advanced to step 2 for full-text review. Further, 127 full-text studies were divided and

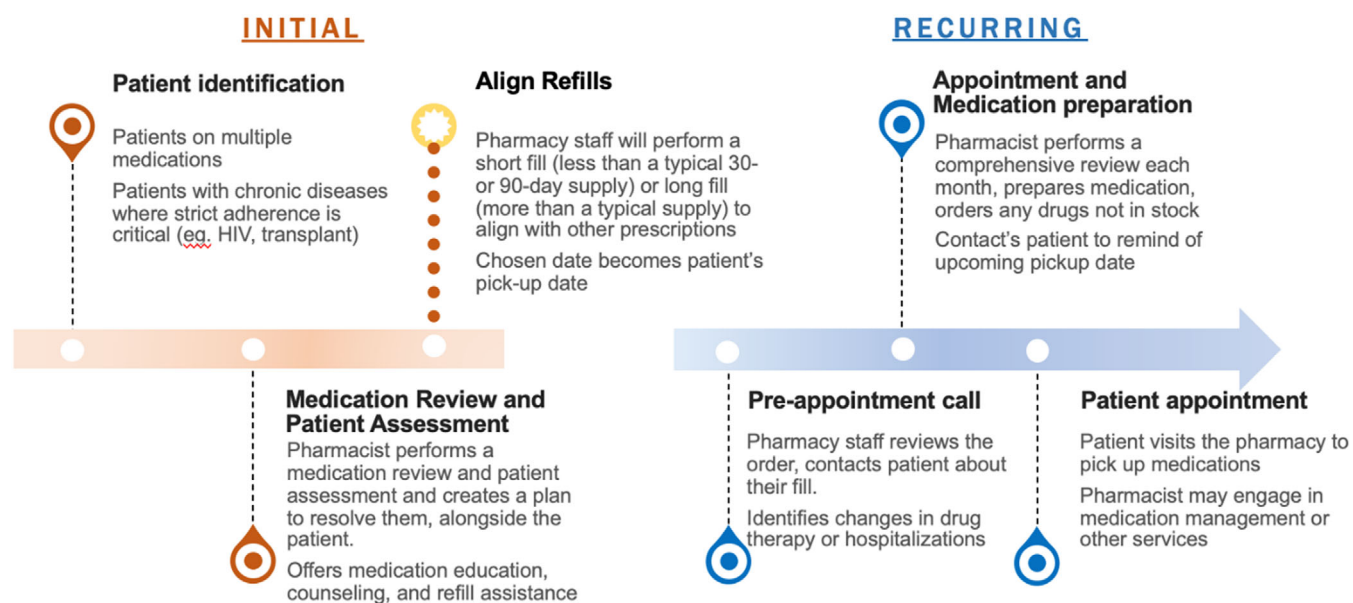


FIGURE 1 Components of med-sync.

TABLE 1 Inclusion and exclusion criteria of study.

Inclusion	Exclusion
Human studies	Animal Studies
Studies having other interventions such as medication reconciliation, patient education, home delivery of medications or Medication Therapy Management intervention along with medication synchronization (med-sync). Studies that included at least one clinical, economic, or humanistic outcome in med-sync.	Studies not having med-sync as their intervention and measuring clinical, economic, or humanistic outcomes.
Full text in English	Full text in languages other than English
Intervention conducted on January 1, 2008 or later	Intervention conducted prior to January 1, 2008
Studies set in the United States of America	Studies set outside of the United States of America
All types of study designs were included such as case studies, case control studies, randomized control trials, cohort studies, published reports by pharmacy organization	Editorials, newspaper articles, conference abstracts, review articles and posters

reviewed independently by two researchers and the reasons for exclusion were noted (Figure 2).¹³ A non-systematic search was done through Google Search using the term “Medication synchronization” from 2008 to 2022 and the titles were evaluated to find additional studies. Reviewers resolved conflicts by consulting two other team members. Data were extracted independently by two researchers and then combined after extraction.

We used PICOTS typology (Patient population, Intervention, Comparator, Outcomes, Timing, Setting) to structure study selection criteria.¹⁴

2.1 | Patient population

Inclusion criteria involved human studies of all age groups and disease states, enrolled or observed in med-sync studies. All types of study designs were included, such as case studies, case-control studies, randomized control trials, cohort studies, and published reports by pharmacy organizations.

2.2 | Intervention

Med-sync, or appointment-based medication synchronization (ABMS), was our intervention of interest. Med-sync is defined as a program that aligns patients' monthly or quarterly chronic medications to a

predetermined single pickup date at a community pharmacy.^{6,15} This is interchangeably used as prescription synchronization or refill synchronization.

ABMS was defined as med-sync programs implemented to enhance automatic syncing; wherein the med-sync program goes beyond automatic refills.¹⁵ Each patient enrolled in the ABM has a designated appointment day to pick up all medications and it may introduce supportive clinical services such as medication reviews performed by the pharmacist.^{15,16}

2.3 | Comparator

For cohort studies, the control group was either not enrolled in a med-sync program or did not have their medications scheduled for a single monthly pickup date. For pre-post studies having no comparator groups, the baseline values were measured against the post-intervention values.

2.4 | Outcomes

The outcomes were based on a modified definition the Economic, Clinical, and Humanistic Outcomes Model, where healthcare utilization was included.¹⁷

Economic and utilization outcomes (UT)—Healthcare utilization and health status are used to examine how efficiently a healthcare system produces health in a population.¹⁷ Health utilization outcomes included medical facility admissions measured as the number of visits/days of hospitalization, number of hospital readmissions, visits to the pharmacy, and prescription volume (refills). For Economic Outcomes, costs were indirect and direct cost of health services measured in US dollars.

Clinical outcomes (CL)—Clinical outcomes are measurable changes in health, function, or quality of life that result from care which can be patient-reported outcomes (PRO), observer-reported, or clinician-reported outcomes.¹⁸ In this review, clinical outcomes included patient adherence measured through proportion of days covered (PDC), medication possession ratio (MPR), measurement of vitals or laboratories such as blood pressure, blood glucose, or viral load.

Humanistic outcomes (HU)—These are clinically meaningful patient-centered outcomes with practical implications for disease recognition and management.¹⁷ They include reporting of outcomes based on a patient's unique perspective. For example, health-related quality of life or patient satisfaction. In this review, humanistic outcomes included patient satisfaction measured via Likert-type scales or categorical scales.

2.5 | Timing

Studies were included if they were conducted, after January 2008 and evaluated the impact of med-sync on at least one of the three

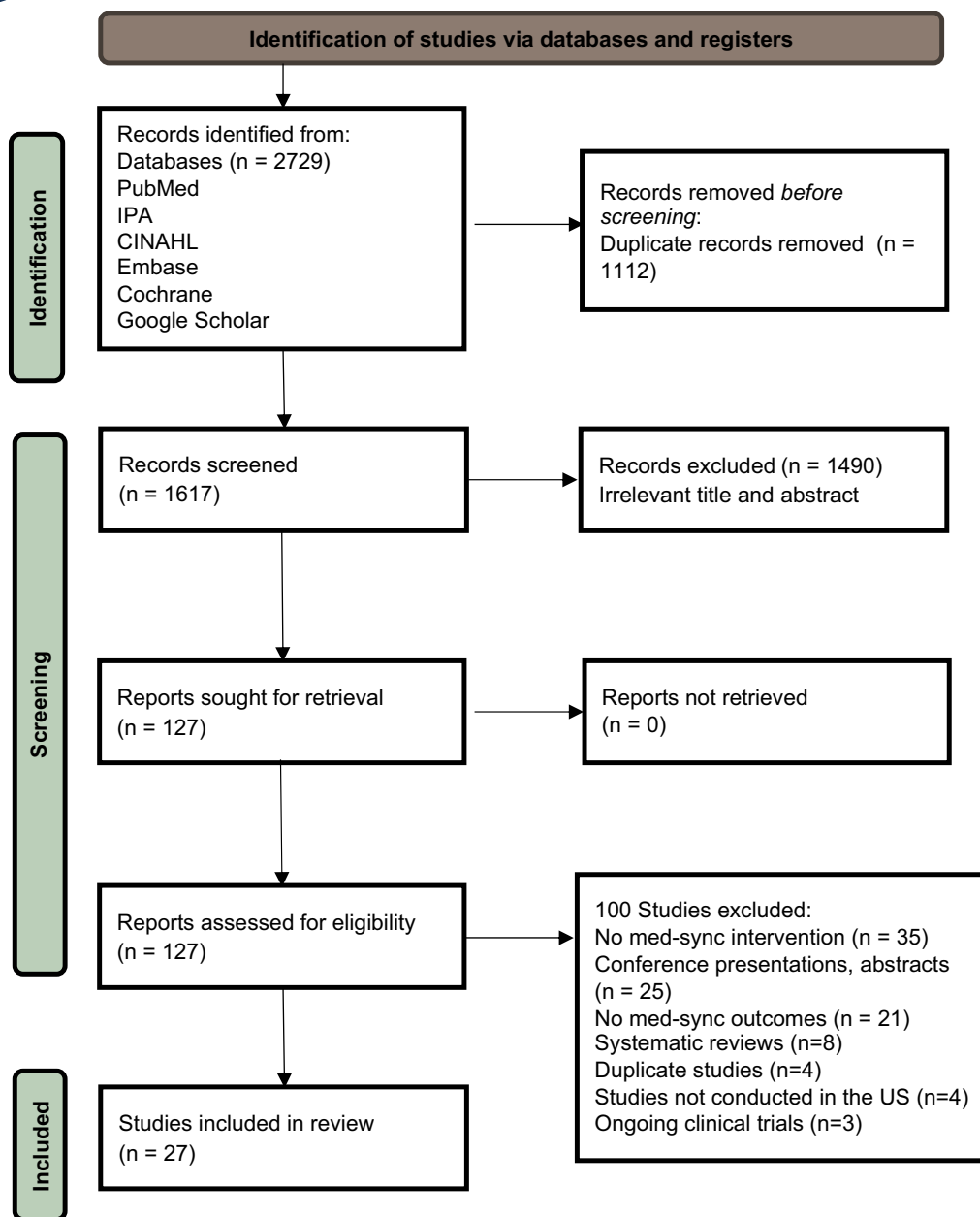


FIGURE 2 Flow diagram for new systematic reviews for study selection retrieval reporting and reports of included studies. CINAHL, Cumulated Index to Nursing and Allied Health Literature; IPA, International Pharmaceutical Abstracts. From Ref. 13.

types of outcomes of interest. The first search was run until April 2, 2021, and another search was re-run on October 15, 2022. The Center for Medicare and Medicaid Services (CMS) started issuing star ratings (1–5 stars) in 2007 to measure pharmacy performance among Medicare Part D plans.^{19–21} Therefore, the starting date of January 2008 was chosen to capture outcomes observed after the CMS implemented star ratings to measure pharmacy performance.

2.6 | Setting

Ambulatory settings (e.g., outpatient clinics or private physician offices), long-term-care settings, or retail pharmacy settings in the

United States. The med-sync service may be delivered in-person, via telephone or video conferencing.

The data elements that were extracted from included studies were study design, start and end dates of med-sync program evaluations, type of pharmacy (independent, chain, mail-order, and unknown), name of the pharmacy/claims, type of study setting (single center vs. multicenter), number of participants, study location, type of med-sync (med-sync, ABM, and other).

After data extraction, risk of biases was assessed to score the strengths and weaknesses of individual studies. A quality assessment template was created using Cochrane's risk of bias tools to grade the studies. ROBINS-1²² scale was used for risk of bias in non-randomized studies of interventions and ROBINS-2²³ scale was used for risk of

TABLE 2 Clinical outcomes studies of medication adherence using time as a control.

Dao, 2018, 12 months pre and post				
Therapy	n	Pre	Post	p Value
Cholesterol reducing agent (Statin)	36	76.44	80.99	<0.001
Antidiabetic agents	37	76.06	81.39	<0.001
RASA (ACE-I/ARB)	8	76.79	81.94	0.002
Witry, 6 months pre and post, PDC				
Therapy	n	Pre	Post	p Value
Antidiabetic agents	13	0.91	0.98	NS
Girdish, 120 days pre and post, days of therapy				
Therapy	n	Pre	Post	p Value
Patients given telephonic calls	126 597	42.6	79.1	NS
Hinson, 2016, 6 months pre and post				
Therapy	n	Pre	Post	Difference
Cholesterol reducing agents	NS	0.861	0.931	NS
Antidiabetic agents	NS	0.874	0.969	NS
RASA (ACE-I/ARB)	NS	0.921	0.931	NS
Dao, 2018, 6 months pre and post				
Therapy	n	Pre	Post	p Value
Cholesterol reducing agent (Statin)	37	76.45	79.18	<0.001
Antidiabetic agents	39	75.88	80.64	<0.001
RASA (ACE-I/ARB)	8	76.79	82.73	0.001

Abbreviations: ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; NS, not specified; PDC, proportion of days covered; Pre, adherence in pre-intervention period; Post, adherence in post-intervention period; RASA, renin-angiotensin-system antagonist.

bias in randomized trials (Table B1). Each of these assessments was conducted independently by two members of the research team.

3 | RESULTS

The search resulted in 1617 studies, after excluding duplicate studies. Ultimately, 127 studies were screened for full-text review, and finally, 27 studies were included in the systematic review (Figure 2). Characteristics of included studies are provided in Table C1. Study designs varied, with 1 (4%) randomized controlled trial,²⁴ 3 (11%) quasi-experimental studies,^{7,25,26} 10 (41%) retrospective cohort studies,²⁷⁻³⁶ 4 (15%) pre-post studies,³⁷⁻⁴⁰ 1 (4%) prospective cohort study,⁴¹ 1 (4%) cost-benefit analysis,⁴² 6 (19%) cross-sectional surveys,⁴³⁻⁴⁸ and 1 (4%) chart review.¹⁰ Med-sync was provided at different pharmacy settings, such as independent, chain, outpatient, and mail-order pharmacies.

Of the 27 studies, 26 were observational and had moderate to serious bias due to confounding and bias in selection of participants for the study (Table B1).^{7,10,24-41,43-47} All the non-randomized studies had a moderate bias in measurement of outcomes, while two studies had serious bias in measurement of outcomes.^{42,48} Confounding was commonly seen as most of the med-sync programs were in

conjunction with other programs, such as Medication Therapy Management (MTM), home delivery services, medication reconciliation, adherence packaging, or educational interventions. Bias of selection of participants was common to retrospective cohort studies, which used synchronized fill dates or refill consolidation methods to create cohorts. We did not exclude any study as there is no generalized definition or implementation method for med-sync.

3.1 | Utilization and cost outcomes

There were studies that measured only utilization ($n = 3$),^{26,34-36,40,41,43,44} costs ($n = 1$),⁴² or both costs and utilization ($n = 1$).^{33,36} Utilizations were measured as hospital admissions,⁴⁰ readmissions,³⁶ emergency department visits,⁴⁰ pharmacy prescription fills/volume,^{26,33,44} number of visits to the pharmacy,³⁵ and vaccination administration.^{41,43}

One study of the Access Program involving medication reconciliation, med-sync, and home visits showed a 76% reduction in 30-day hospital readmission rates, reducing readmissions from the national average of 17.3 readmissions per 100 patients to 4.1 per 100 patients. This reduction generated a potential healthcare savings of \$1478 per patient compared with national averages.³⁶ Another study examined

TABLE 3 Clinical outcomes studies of medication adherence with a cohort control group.

	Control patients			Study patients			Effect measure (D)	p
	Mean adherence	SD	N	Mean adherence	SD	N		
Holdford, 2013, quasi-experimental								
RASA (ACEIs/ARBs)	0.61	0.318	537	0.87	0.216	278	0.26	<0.0001
Anti-hypertensives (Beta blocker)	0.61	0.312	415	0.84	0.227	202	0.23	<0.0001
Calcium channel blockers (DCCBs)	0.63	0.306	196	0.82	0.255	106	0.19	<0.0001
Thiazide diuretics	0.58	0.328	100	0.8	0.269	59	0.22	0.001
Antidiabetic agents (Metformin)	0.62	0.295	87	0.86	0.233	47	0.24	0.001
Cholesterol lowering agent (Statins)	0.62	0.289	564	0.84	0.248	281	0.22	<0.0001
Holdford, 2015, retrospective cohort								
RASA (ACEIs/ARBs)	0.71	0.301	1133	0.91	0.225	584	NS	<0.001
Anti-hypertensives (Beta blocker)	0.64	0.324	856	0.78	0.277	452	NS	<0.001
Calcium channel blockers (DCCBs)	0.62	0.329	418	0.81	0.288	246	NS	<0.001
Thiazide diuretics	0.58	0.341	687	0.77	0.284	385	NS	0.001
Antidiabetic agents (Metformin)	0.57	0.338	232	0.73	0.28	140	NS	0.006
Cholesterol lowering agents (Statins)	0.63	0.313	1197	0.8	0.259	600	NS	<0.001
Painter, 2015, retrospective cohort								
Anti-hypertensives (Beta blockers)	0.73	0.256	9569	0.85	0.199	1971	0.12	<0.001
Antidiabetic agents (Biguanides)	0.71	0.255	4666	0.84	0.206	1039	0.13	<0.001
Calcium channel blockers	0.75	0.255	6450	0.87	0.188	1351	0.12	<0.001
Antidiabetic agents (DPP-IV inhibitors)	0.69	0.271	241	0.83	0.216	108	0.14	<0.001
Non-warfarin anticoagulants	0.68	0.277	219	0.83	0.22	103	0.15	<0.001
RASA	0.75	0.249	13 346	0.86	0.185	2707	0.11	<0.001
Cholesterol reducing agents (Statins)	0.74	0.249	12 092	0.86	0.197	2465	0.12	<0.001
Antidiabetic agents (Sulfonylureas)	0.75	0.24	2236	0.84	0.196	598	0.09	<0.001
Ghassemi, 2018, retrospective cohort								
Antiretroviral	0.71	0.1	29	0.96	0.4	29	NS	<0.001
Krumme, 2018, retrospective cohort								
Cardiovascular	0.84	NS	6519	0.87	NS	16, 286	NS	<0.001
Doshi, 2017, retrospective cohort								
Anti-hypertensives	0.94	NS	NS	0.92	NS	5726	0.02	<0.01
Cholesterol reducing agent	0.91	NS	NS	0.92	NS	3444	0.06	<0.02
Antidiabetic agents	0.9	NS	NS	0.87	NS	547	0.03	<0.03
Antidepressants	0.9	NS	NS	0.83	NS	398	0.07	<0.04
Antiosteoporotic agents	0.85	NS	NS	0.81	NS	123	0.04	0.11

Abbreviations: ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; DCCB, dihydropyridine calcium channel blocker; NS, not specified; RASA, renin-angiotensin-system antagonist.

healthcare utilization in the AtHome program which included med-sync, adherence packaging, and home delivery services.⁴⁰ This study found a reduction in emergency department visits accounted for most of the hospital visit-related benefit for this program, with a risk reduction of 33% after enrollment, but a minimal change in unplanned hospitalizations occurred.⁴⁰ Conversely, a study of pharmacies in Maine did not find any significant differences in cost savings for either medical or pharmacy costs in Medicare Advantage (MA-PD) patients taking statin, renin-angiotensin system antagonist (RASA), or noninsulin diabetes medications.³³

For pharmacy utilization, in a study of Midwest pharmacies, there was an increase in the number of fills by 9%–19% from 6-month pre-med-sync enrollment period to 6-month post-med-sync enrollment period for patients on diabetes, hypertension, and hyperlipidemia medications.³⁵ Another study of pharmacies in the North Carolina Community Pharmacy Enhanced Services Network showed that pharmacies that adopted med sync were more likely to be independently owned and have a clinical pharmacist on staff.⁴⁴ In the study group, there was no difference in the number of med-sync and non-med-sync pharmacies having a prescription volume of less than 2000 a

TABLE 4 Clinical outcomes studies of medication adherence using a cohort and time control.

	Med sync			Non-med sync			Estimate	95% CI
	N	Pre	Post	N	Pre	Post		
Doshi, 2016, quasi-experimental ⁹								
Anti-hypertensives	653	86%	89%	660	84%	84%	0.03	0.02, 0.04
Cholesterol-lowering drugs	549	71%	78%	536	66%	0.69%	0.04	0.03, 0.06
Antidiabetic agents	215	70%	80%	211	72%	0.76%	0.05	0.03, 0.08
Andrews, 2017, quasi-experimental								
Antidiabetic agents	34	91%	100%	34	91%	74%	NS	NS
RASA	97	92%	98%	97	92%	80%	NS	NS
Cholesterol lowering agents (statins)	84	83%	98%	84	83%	75%	NS	NS
Singleton, 2017, prospective study (3 months)								
Overall	12	63%	82%	13	67%	76%	Not significant	NS

Abbreviations: CI, confidence interval; Med-Sync, medication synchronization; NS, not specified; Post, adherence in post-intervention period; Pre, adherence in pre-intervention period; RASA, renin-angiotensin-system antagonist.

^aTo help with interpretation in our table, pre and post adherence was converted to a percentage. In this paper, the authors reported adherence as a proportion.

week.⁴⁴ A study with a national chain-pharmacy showed that the average number of pharmacy visits per patient declined by only 0.17 visits from baseline (120 days pre-enrollment) to 120 days post-enrollment.³⁵ Similarly, in another national study, the increase in the number of fills after enrollment ranged from 7.5 to 14.8 more prescriptions within the 6-month period.³⁴ In this study, the number of trips after enrollment decreased from 4.5 to 1.9 fewer trips for face-to-face and hybrid (telephonic as well as pharmacy), respectively.

Finally, vaccination utilization increased when patients were introduced to med-sync.^{41,43} The mean number of vaccinations administered per store during the study time frame was 1810 ± 500.88 in the intervention stores compared with 1455 ± 754.43 in the control stores ($p = 0.01$). In addition, there were significantly more vaccinations given for herpes zoster in the intervention stores compared with the control stores (166.90 vs. 130.10; $p = 0.04$).⁴¹

3.2 | Clinical outcomes

A total of 21 studies with clinical outcomes were identified.^{7,10,24-35,37-39,43-46} Out of these studies, adherence was the most commonly measured outcome ($n = 16$).^{7,24-26,28-33,35,37-39,44-46} The study group size ranged from 8 to 126 597. Results of the studies were divided based on study designs. In studies using time as a control, there was an increase in adherence from pre to post-measurement (Table 2).^{25,26,33,35,38,39} In studies having a control cohort, the med-sync group had a significantly higher adherence to medications compared to the non-med sync group^{7,24,26,28,30-33,35,37} and less synchronized group (Table 3).^{29,45} Other studies using both a cohort and time, showed an increase in adherence from pre to post-measurement (Table 4).^{25,26,33,35,38,39} Medication classes most commonly used to measure adherence were anti-hypertensives (beta-blockers), RASA (angiotensin-converting enzyme-1/angiotensin II receptor blockers [ACE-I/ARB]), noninsulin oral antidiabetics (e.g., Metformin), thiazide

diuretics, calcium channel blockers, and cholesterol-lowering agents (Statins). In the only randomized study in this review, blood pressure was measured as an outcome for patients on hypertension medications.²⁴

The majority of study designs showed a significant increase ($p < 0.001$) in adherence after enrollment compared with the comparison group (Tables 2-4). Not all studies reported a statistically significant increase in adherence. In one study, med-sync adoption was not significantly associated with total medication adherence performance ($p = 0.371$).⁴⁴ Another study indicated that PDC showed a significant increase in statin and angiotensin receptor blockers (ARBs) from pre to 6 months post studies ($p \leq 0.001$), but PDC of oral diabetes medications did not show a significant increase in 6 months post-study.³⁹ In another study among patients taking oral diabetes medications, there was not a significant increase in PDC scores in 120 days post med-sync intervention.³⁷

Apart from adherence, two studies measured identification of drug therapy problems (DTPs).^{10,43} In a chart review study of pharmacist notes having ABM programs evaluated over a period of 1 month found that 74.2% of ABM participants had at least one DTPs identified during their encounter. The most common DTPs identified were needing additional drug therapy (43.1%), inappropriate adherence (31.4%), unnecessary drug therapy (15.0%), and adverse drug reaction (9.6%). Interventions for potential adverse drug reactions were managing a high-risk drug for patient, prescription counseling, scheduling, or completing an MTM appointment, addressing adherence issue, managing drug-drug interaction, and evaluating prescription drug monitoring programs.

3.3 | Humanistic outcomes

There were four studies that evaluated humanistic outcomes of patient or provider satisfaction of med-sync programs. Three studies conducted surveys at a single pharmacy location⁴⁶⁻⁴⁸ and one study

had multiple locations (24 pharmacies).⁴¹ Patient satisfaction and pharmacist satisfaction through med-sync service were measured through pre-validated surveys or modified surveys. Two studies used existing validated surveys with modifications^{47,48} while two studies developed a survey.^{41,46} All of the studies used cross-sectional surveys for med-sync outcomes. Three studies measured patient satisfaction^{46–48} while one study measured both patient and pharmacist satisfaction.⁴¹ The methods to administer survey were print,^{41,46,47} email,⁴¹ or telephonic.⁴⁸

Diabetes Disease State Management Questionnaire survey statements were modified to reflect the med-sync program Time My Meds (TMM) as the service instead of diabetes disease state management. This survey was distributed 3 months after the patients enrolled in med-sync program. Participants were highly satisfied with TMM and their comments were generally positive, indicating that TMM was convenient and increased accountability ($n = 48$).⁴⁷ Positive outcome of this study led the chain pharmacy to expand this program to 20 pharmacies.

Another study utilized an 8-item survey developed by the researchers for patient satisfaction after med-sync intervention.⁴⁶ This survey used a performance orientation scale focusing on recruitment approach, patient interest, targeting criteria, and patient satisfaction. The program allowed patients to be enrolled in both diabetes education and a med-sync program ($n = 43$). Participants ($n = 25$) agreed or strongly agreed that med-sync intervention saves time (96%) and that they would recommend the program (88%). Two participants, however, disagreed that the program fit with their budget.

Another study used a face and content validated survey for patient and pharmacist perceptions of the ABM in terms of their vaccination experience ($n = 96$).⁴¹ More than 90% of patients who completed this survey would recommend the program and would recommend the pharmacy because of the program. More than 80% of pharmacists stated that the program facilitated ongoing relationships with patients, and more than 50% stated that the program allowed them to provide more counseling and MTM services.⁴¹

In a final study, survey questions were informed by the Patients' Lived Experience with Medicines framework using three broad domains of medication-related burden, medication-related beliefs, and medication taking practice and a fourth domain with patients' perceived quality of life ($n = 42$).⁴⁸ This study found that 88% of patients enrolled in comprehensive medication adherence packaging service which included med-sync reported missing fewer doses and 76% reported they were more likely to take their medications on time.

4 | DISCUSSION

This study discussed economic, utilization, clinical, and humanistic outcomes of patients enrolled in med-sync. Studies show a common theme that med-sync improves adherence, and reduces time⁴⁶ and trips to the pharmacy as well as positive humanistic outcomes.^{33,34}

We would assume that an increase in medication adherence and increased medication refills would increase medication costs to the patients, but current studies in the literature have mixed results for

med-sync. In one study, there was no significant increase in pharmacy costs from health plans perspective for patients enrolled in med-sync.³³ Another study showed no difference in utilization as well as pharmacy cost for med-sync and non-med-sync patients.⁴⁴ In contrast, a study in rural-Midwest showed higher utilization of medications but lower monthly average patient out-of-pocket cost per fill.³⁵ Another study of a national-pharmacy chain has shown an increase in number of fills and number of vaccinations due to med-sync, although pharmacy costs were not studied.³⁴ The reasons for variation in pharmacy utilization and cost is unclear but may be due to the variation in the type of med-sync program provided.

There were only two studies that focused on the medical costs associated with med sync. Cost-benefit studies calculated an additional medication cost from higher number of annual medication refills, but lower medical costs.⁴² However, these costs were derived based on average cost of medication fills, adherence, and disease-related medical costs available in literature, and not directly through pharmacy prescription claims or medical claims of patients.⁴² Another study observed a reduction in hospital costs for patients in a transition of care program which included medication reconciliation, med-sync, and home visits program.³⁶ Here, the all-cause hospitalizations costs in the transitions of care program were compared to national averages.³⁶ Since this study has multiple interventions, we cannot estimate if the lower costs are contributed by any one intervention or through the effect of all interventions together. In both of the studies, there is no cost comparison between med-sync and non-med-sync groups.^{36,42} More research needs to be conducted to measure per capita cost of healthcare through the supply lens of providers; the demand lens of patients; and the intermediary lens of health plans and insurers.⁴⁹ Future research is warranted with medical and pharmacy claims to determine whether med-sync prevents hospitalizations and reduces cost.

The findings from our systematic review suggest that while considerable heterogeneity is present in the measurement of medication adherence, the adherence improved across most studies.^{7,24,26,28–33,35,37} We considered PDC and MPR as clinical outcomes although they are surrogate markers for adherence, which can be used as a substitute for clinical endpoints. Our findings are consistent with two other published systematic reviews that examined clinical outcomes of medication adherence.^{50,51} In the first of these reviews, a meta-analysis of nine studies found an increase in medication adherence (associated with 2.29 times higher odds of adherence) similar to our systematic review study with an increase of 1%–36.5% in studies using time as control and 2%–26% in studies using a cohort control group. ABM med-sync studies had the highest impact on adherence. The second review of six studies also found improvement in medication adherence.^{24,29,38,39,45} Our review extended the findings from the previous two studies and supported improved adherence across almost all studies. However, a non-significant increase in adherence was found for oral antidiabetic medications after 120 days from the first interaction with the pharmacist.^{37,39} Subsequently, one of these studies found a significant increase in PDC 6 and 12 months post-enrollment.⁴¹

Adherence-related outcomes are congruent with CMS Part D star ratings measures around medication adherence.^{19–21} As a result, med

sync programs have grown since 2008 when star ratings were implemented as a method for assessing the quality of care provided by pharmacies. We found that different types of services used med-sync as an intervention in the studies. Appointment-based model, Simplify My Meds, Script your future, Sona Access, and CVS script Sync were some of the services offered in pharmacies. In one study, having a clinical pharmacist on site (vs. not having a clinical pharmacist) did not affect pharmacy performance scores.⁴⁴ This variability in med-sync programs likely affects the overall measurable healthcare outcomes. The literature has discussed strategies for implementing a standardized and effective med-sync process.^{11,52} To ensure consistency and optimal outcomes, it is essential that the med-sync process consistently follows the pharmacists' patient care process, which involves thorough patient assessment, medication review, and continuous monitoring for potential drug-related issues.

Although other previous research has demonstrated a positive impact of medication adherence on clinical outcomes, such as blood pressure,⁵³ the only randomized study measuring this outcome in our review found no significant increase in systolic or diastolic blood pressure between patients on hypertension medications who participated in med-sync programs and those who did not.²⁴ Despite the considerable evidence that med sync programs improve medication adherence, there is limited evidence about the effect of med sync on other clinical endpoints such as lipids, asthma control,⁵⁴ or A1c. These studies can be carried out using clinical electronic health records and/or through prospective clinical trials. Clinical trials would also reduce confounding and the high risk of bias due to non-randomized selection of participants in the study, which we discovered in most of the studies from this review. Some studies overcame selection bias by using a quasi-experimental study design, using a treatment and a control cohort, as well as a pre-posttest to account for time. It is also unknown if med-sync services reduce adverse drug events. Future studies should examine med sync in the context of these types of clinical outcomes.

Additionally, our systematic review examined four studies of humanistic outcomes which were not included in previous systematic reviews.^{41,46-48} These studies varied in both the population studies and their approach to measuring outcomes. Some studies assess patient-related measures, while others measure the pharmacist's perspective. These studies utilized a variety of questionnaires and instruments to assess patient satisfaction,^{41,47} pharmacist satisfaction,⁴¹ affective and performance orientation,⁴⁶ self-reported medication-taking behaviors,⁴⁸ confidence in managing their medications,⁴⁸ and perceived quality of life.⁴⁸ Participants' comments were generally positive towards med-sync use. Overall, the studies found a high degree of both patient and pharmacist satisfaction with med sync programs. These humanistic outcomes are congruent with other evidence that med sync improves workflow for the pharmacy, improves the quality of pharmacy care, and reduces trips to pharmacy for patients.

4.1 | Limitations

Some studies are unlikely to have clearly formed research questions, participants, or outcomes and they were marked as having a high risk

of bias.^{42,48} Heterogeneity was present between studies given the variation between the components of med-sync in each pharmacy. Most studies had small sample sizes and many of the included studies reported on interventions that had a short follow-up period (3 months). Other studies were performed as a quality assurance or performance improvement projects for existing med-sync programs through customer evaluations. This may inevitably impact the completeness of the study information and results. There is a clear need for more prospective and controlled trials of med-sync.

5 | CONCLUSION

Overall, this systematic review explored and quantified clinical, costs, healthcare utilization, and humanistic outcomes of med-sync programs. This review found limited studies related to costs and healthcare utilization. There is a need to study the long-term health outcomes of patients enrolled in med-sync program. Pharmacy programs that include med-sync as one of their services have shown to improve hospital utilization and reduce costs. There are mixed results for med-sync services in improving pharmacy fills and prescription utilization. Med-sync programs have shown to increase drug adherence to medications. Med-sync interventions have increased patient satisfaction and pharmacist have commented that it leads to more counseling and MTM services. Future studies should evaluate patient satisfaction and quality of life after enrolling in med-sync.

ACKNOWLEDGMENTS

The authors would like to acknowledge the Community Pharmacy Foundation (Grant #170) and the Purdue University College of Pharmacy Department of Pharmacy Practice for financial support.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest. Dr. Zillich is a JACCP associate editor.

DATA AVAILABILITY STATEMENT

Data sharing not applicable—no new data generated, or the article describes entirely theoretical research.

ORCID

Prajakta H. Waghmare  <https://orcid.org/0000-0001-8442-2216>

Alan J. Zillich  <https://orcid.org/0000-0002-7495-3678>

REFERENCES

- McDonnell PJ, Jacobs MR. Hospital admissions resulting from preventable adverse drug reactions. *Ann Pharmacother*. 2002;36(9):1331-6. <https://doi.org/10.1345/aph.1A333>
- Fischer MA, Stedman MR, Lii J, Vogeli C, Shrank WH, Brookhart MA, et al. Primary medication non-adherence: analysis of 195,930 electronic prescriptions. *J Gen Intern Med*. 2010;25(4):284-90. <https://doi.org/10.1007/s11606-010-1253-9>
- Rasmussen JN, Chong A, Alter DA. Relationship between adherence to evidence-based pharmacotherapy and long-term mortality after

- acute myocardial infarction. *JAMA*. 2007;297(2):177–86. <https://doi.org/10.1001/jama.297.2.177>
4. Hoffman A, Emanuel EJ. Reengineering US health care. *JAMA*. 2013; 309(7):661–2. <https://doi.org/10.1001/jama.2012.214571>
 5. Institute for Safe Medication Practices (ISMP). Improving medication safety in community pharmacy: assessing risk and opportunities for change. Published 2009. Available from: https://www.ismp.org/sites/default/files/attachments/2018-02/ISMP_AROC_whole_document.pdf. Accessed 1 Aug 2022.
 6. American Pharmacists Association. Leveraging the appointment-based model to expand patient care services. Published online September 2018. Available from: https://aphanet.pharmacist.com/sites/default/files/files/APhA_Leveraging_the_Appointment_Based_Model.pdf
 7. Holdford DA, Inocencio TJ. Adherence and persistence associated with an appointment-based medication synchronization program. *J Am Pharm Assoc*. 2013;53(6):576–83. <https://doi.org/10.1331/JAPhA.2013.13082>
 8. APhA Foundation. Align my refills. APhA Foundation. Available from: <https://www.aphafoundation.org/align-my-refills>. Accessed 7 Jul 2022.
 9. Pennsylvania Association of Chain Drug Stores (PACDS), Pennsylvania Pharmacists Association (PPA), Value Drug Company, Philadelphia Association of Retail Druggists (PARD). What is Medication Synchronization? Available from: https://cdn.ymaws.com/www.papharmacists.com/resource/resmgr/legislative/MedSync/HOUSE_MedSync_IssueBrief.pdf
 10. Fitzpatrick RM, Witry MJ, Doucette WR, Kent K, Deninger MJ, McDonough RP, et al. Retrospective analysis of drug therapy problems identified with a telephonic appointment-based model of medication synchronization. *Pharm Pract*. 2019;17(2):1373. <https://doi.org/10.18549/PharmPract.2019.2.1373>
 11. Renfro CP, Patti M, Ballou JM, Ferreri SP. Development of a medication synchronization common language for community pharmacies. *J Am Pharm Assoc*. 2018;58(5):515–521.e1. <https://doi.org/10.1016/j.japh.2018.04.032>
 12. Covidence systematic review software. Available from: www.covidence.org
 13. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71.
 14. FDA (U.S. Food and Drug Administration). Using the PICOTS framework to strengthen evidence gathered in clinical trials—guidance from the AHRQ's Evidence-Based Practice Centers program. Available from: <https://www.fda.gov/media/109448/download>. Accessed 27 Mar 2023.
 15. Watson L, Bluml B. *Pharmacy's appointment based model: implementation guide for pharmacy practice*. Washington, DC: APhA Foundation; 2013. Available from: <https://www.aphafoundation.org/sites/default/files/ckeditor/files/ABMImplementationGuide-FINAL-20130923.pdf>. Accessed 10 Oct 2021.
 16. Watson L. *Pharmacy's appointment based model: a prescription synchronization program that improves adherence*. Washington, DC: APhA Foundation; 2013. Available from: <https://naspa.us/wp-content/uploads/2015/07/ABMWhitePaper-FINAL-201309233.pdf>. Accessed 10 Oct 2022.
 17. Kozma CM, Reeder CE, Schulz RM. Economic, clinical, and humanistic outcomes: a planning model for pharmaco-economic research. *Clin Ther*. 1993;15(6):1121–32. discussion 1120.
 18. Great Ormond Street Hospital (GOSH). Clinical outcomes. Available from: <https://www.gosh.nhs.uk/conditions-and-treatments/clinical-outcomes/#:~:text=Clinical%20outcomes%20are%20measurable%20changes,all%20aspects%20of%20our%20practice>. Accessed 9 Jan 2022.
 19. Navitus Health Solutions. Aligning with the right PBM: why Medicare star ratings matter. Navitus: pharmacy benefits reinvented. Published 21 May 2021. Available from: <https://blog.navitus.com/star-ratings-2021>. Accessed 25 May 2021.
 20. CMS.gov. Part C and D performance data. CMS.gov. Published 5 Aug 2022. Available from: <https://www.cms.gov/Medicare/Prescription-Drug-Coverage/PrescriptionDrugCovGenIn/PerformanceData>. Accessed 22 Aug 2023.
 21. Centers for Medicare & Medicaid Services. Enhanced tools will help Medicare beneficiaries with prescription drug plan choices for 2008. CMS.gov. Published 2007. Available from: <https://www.cms.gov/newsroom/press-releases/enhanced-tools-will-help-medicare-beneficiaries-prescription-drug-plan-choices-2008>
 22. Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ*. 2016;355:i4919. <https://doi.org/10.1136/bmj.i4919>
 23. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ*. 2019;366:i4898.
 24. DiDonato K, Vetter K, Liu Y, May J, Hartwig D. Examining the effect of a medication synchronization or an education program on health outcomes of hypertensive patients in a community pharmacy setting. 2014; 5(3). <https://doi.org/10.24926/iip.v5i3.357>
 25. Doshi JA, Lim R, Li P, Young PP, Lawnicki VF, State JJ, et al. A synchronized prescription refill program improved medication adherence. *Health Aff*. 2016;35(8):1504–12. <https://doi.org/10.1377/hlthaff.2015.1456>
 26. Andrews SB, Marcy TR, Osborn B, Planas LG. The impact of an appointment-based medication synchronization programme on chronic medication adherence in an adult community pharmacy population. *J Clin Pharm Ther*. 2017;42(4):461–6. <https://doi.org/10.1111/jcpt.12533>
 27. Painter JT, Moore G, Morris B. Addressing medication non-adherence through implementation of an appointment-based model synchronization network. Published online 2015.
 28. Ghassemi E, Smith J, Owens L, Herring C, Holland M. Relationship between medication synchronization and antiretroviral adherence. *J Am Pharm Assoc*. 2018;58(4):S78–82. <https://doi.org/10.1016/j.japh.2018.05.002>
 29. Neuner JM, Fergestrom NM, Laud PW, Nattinger AB, Beyer KMM, Flynn KE, et al. The association of pharmacy fill synchronization with breast cancer endocrine therapy adherence. *Cancer*. 2019;125(22):3960–5. <https://doi.org/10.1002/cncr.32433>
 30. Krumme AA, Glynn RJ, Schneeweiss S, Gagne JJ, Dougherty JS, Brill G, et al. Medication synchronization programs improve adherence to cardiovascular medications and health care use. *Health Aff*. 2018;37(1):125–33. <https://doi.org/10.1377/hlthaff.2017.0881>
 31. Doshi JA, Lim R, Li P, Young PP, Lawnicki VF, Troxel AB, et al. Synchronized prescription refills and medication adherence: a retrospective claims analysis. *Am J Manag Care*. 2017;23(2):98–104.
 32. Holdford D, Saxena K. Impact of appointment-based medication synchronization on existing users of chronic medications. *J Manag Care Pharm*. 2015;21(8):662–9.
 33. Bernard K, Cowles B, McCall K, Henningsen RM, O'Toole M, Tu C. Impact of medication synchronization programs on proportion of days covered (PDC) scores and Medicare part D medication-related adherence metrics. *J Am Pharm Assoc*. 2019;59(3):343–8. <https://doi.org/10.1016/j.japh.2019.02.003>
 34. Barnes B, Hincapie AL, Luder H, Kirby J, Frede S, Heaton PC. Appointment-based models: a comparison of three model designs in a large chain community pharmacy setting. *J Am Pharm Assoc*. 2018; 58(2):156–162.e1. <https://doi.org/10.1016/j.japh.2018.01.005>
 35. Girdish C, Shrank W, Freytag S, Chen D, Gebhard D, Bunton A, et al. The impact of a retail prescription synchronization program on medication adherence. *J Am Pharm Assoc*. 2017;57(5):579–584.e1. <https://doi.org/10.1016/j.japh.2017.05.016>

36. Korn AS, Michaels NM, Phillips D, Rhodes LA, Marciniak MW. Impact of a coordination of care program in an independent community pharmacy. *J Am Pharm Assoc.* 2019;59(4):S141–5. <https://doi.org/10.1016/j.japh.2019.05.020>
37. Singleton J, Veach S, Catney C, Witry M. Analysis of a community pharmacy intervention to improve low adherence rates to oral diabetes medications. *Pharmacy.* 2017;5(4):58. <https://doi.org/10.3390/pharmacy5040058>
38. Hinson JL, Garofoli GK, Elswick BM. The impact of medication synchronization on quality care criteria in an independent community pharmacy. *J Am Pharm Assoc.* 2017;57(2):236–40. <https://doi.org/10.1016/j.japh.2016.11.008>
39. Dao N, Lee S, Hata M, Sarino L. Impact of appointment-based medication synchronization on proportion of days covered for chronic medications. *Pharmacy.* 2018;6(2):44. <https://doi.org/10.3390/pharmacy6020044>
40. Shope CJ, Bruno M, Ruby CM, Naumovski J, Isabella CJ, Aspinall M. Evaluating the effects of a medication adherence packaging program on outcomes in older people. *Sr Care Pharm.* 2022;37(2):73–81. <https://doi.org/10.4140/TCP.n.2022.73>
41. Luder HR, Kunze N, Heaton PC, Frede SM. An appointment-based model to systematically assess and administer vaccinations. *J Am Pharm Assoc.* 2018;58(3):290–5. <https://doi.org/10.1016/j.japh.2018.02.010>
42. Patterson JA, Holdford DA, Saxena K. Cost-benefit of appointment-based medication synchronization in community pharmacies. *Am J Manag Care.* 2016;22(9):587–93.
43. Ariyo O, Kinney O, Brookhart A, Nadpara P, Goode JKR. Medication therapy problems and vaccine needs identified during initial appointment-based medication synchronization visits. *J Am Pharm Assoc.* 2019;59(4):S67–71. <https://doi.org/10.1016/j.japh.2019.04.019>
44. Renfro CP, Turner K, Seeto J, Ferreri SP. Medication synchronization adoption and pharmacy performance. *Res Soc Adm Pharm.* 2020; ((Renfro C.P.) Department Clinical Pharmacy and Translational Science at the University of Tennessee Health Science Center College of Pharmacy, TN, Memphis, United States (Turner K.) FL, Assistant Member at Moffitt Cancer Center and an Assistant Professor a). <https://doi.org/10.1016/j.sapharm.2020.11.009>.
45. Cheng A, Hughes TD, Chen HH, Ozawa S, Ferreri SP. Beyond refill alignment: evaluating the impact of appointment-based model. *Res Social Adm Pharm.* 2022;18(10):3751–7. <https://doi.org/10.1016/j.sapharm.2022.05.004>
46. Witry M, Ernzen M, Pape A, Viyyuri BR. Pilot and feasibility of combining a medication adherence intervention and group diabetes education for patients with type-2 diabetes. *Pharmacy.* 2019;7(3):76. <https://doi.org/10.3390/PHARMACY7030076>
47. Butler KT, Ruisinger JF, Bates J, Prohaska ES, Melton BL. Participant satisfaction with a community-based medication synchronization program. *J Am Pharm Assoc.* 2015;55(5):534–9. <https://doi.org/10.1331/JAPhA.2015.14242>
48. Phi C, Berenbrok LA, Carroll JC, Firm A, McGivney MS, Coley KC. Impact of a medication adherence packaging service on patient-centered outcomes at an independent community pharmacy. *Pharmacy.* 2021;9(1):1–7. <https://doi.org/10.3390/pharmacy9010011>
49. Stiefel M, Nolan K. *A guide to measuring the triple aim: population health, experience of care, and per capita cost.* Boston, MA: Institute for Healthcare Improvement; 2012. Available from: www.IHI.org
50. Nguyen E, Sobieraj DM. The impact of appointment-based medication synchronization on medication taking behaviour and health outcomes: a systematic review. *J Clin Pharm Ther.* 2017;42(4):404–13. <https://doi.org/10.1111/jcpt.12554>
51. Nsiah I, Imeri H, Jones AC, Bentley JP, Barnard M, Kang M. The impact of medication synchronization programs on medication adherence: a meta-analysis. *J Am Pharm Assoc.* 2021;61(4):e202–11. <https://doi.org/10.1016/j.japh.2021.02.005>
52. Patti M, Renfro CP, Posey R, Wu G, Turner K, Ferreri SP. Systematic review of medication synchronization in community pharmacy practice. *Res Social Adm Pharm.* 2019;15(11):1281–8. <https://doi.org/10.1016/j.sapharm.2018.11.008>
53. Choudhry NK, Glynn RJ, Avorn J, Lee JL, Brennan TA, Reisman L, et al. Untangling the relationship between medication adherence and post-myocardial infarction outcomes: medication adherence and clinical outcomes. *Am Heart J.* 2014;167(1):51–58.e5. <https://doi.org/10.1016/j.ahj.2013.09.014>
54. Murphy AC, Proeschal A, Brightling CE, Wardlaw AJ, Pavord I, Bradding P, et al. The relationship between clinical outcomes and medication adherence in difficult-to-control asthma. *Thorax.* 2012; 67(8):751–3. <https://doi.org/10.1136/thoraxjnl-2011-201096>

How to cite this article: Waghmare PH, Lindsey R, Reed JB, Gao S, Zillich AJ Systematic review of the impact of medication synchronization on healthcare utilization, economic, clinical, and humanistic outcomes. *J Am Coll Clin Pharm.* 2023;6(6):597–614. doi:10.1002/jac5.1815

APPENDIX A

TABLE A1 Systematic review search terms.

Source	Search terms
PubMed	#1 (medication[tw] or prescription[tw] or medications[tw] or prescriptions[tw] or refill[tw] or refills[tw])
	#2 (synchronization[tw] or synchronized[tw] or alignment[tw] or aligns[tw] or aligning[tw])
	#3 (#1 and #2)
	#4 (“appointment based”[tw] or (med[tw] and sync[tw]))
	#5 (#3 or #4) AND (2008:2022[pdat])
CINAHL	S1 TI medication OR AB medication OR TI prescription OR AB prescription OR TI medications OR AB medications OR TI prescriptions OR AB prescriptions OR TI refill OR AB refill OR TI refills OR AB refills
	S2 TI synchronization OR AB synchronization OR TI synchronized OR AB synchronized OR TI aligns OR AB aligns OR TI alignment OR AB alignment OR TI aligning OR AB aligning OR TI schedule OR AB schedule OR TI scheduling OR AB scheduling OR TI scheduled OR AB scheduled
	S3 S1 and S2
	S4 TI med sync OR AB med sync OR TI appointment based OR AB appointment based
	S5 (S3 OR S4)
International Pharmaceutical Abstracts (IPA)	#1 ((medication or prescription or medications or prescriptions or refill or refills).ti. or (medication or prescription or medications or prescriptions or refill or refills).ab.)
	#2 ((synchronization or synchronized or alignment or aligns or aligning).ti. or (synchronization or synchronized or alignment or aligns or aligning or schedule or scheduling or scheduled).ab.)
	#3 #1 and #2
	#4 (“med sync” or “appointment based”).ti. or (“med sync” or “appointment based”).ab.)
	#5 #3 or #4
	#6 #5 and 2008:2022.(sa_year).
Embase	#1 (medication:ti,ab,kw OR medications:ti,ab,kw OR prescription:ti,ab,kw OR prescriptions:ti,ab,kw OR refill:ti,ab,kw OR refills)
	#2 (synchronization:ti,ab,kw OR synchronized:ti,ab,kw OR alignment:ti,ab,kw OR aligns:ti,ab,kw OR aligning:ti,ab,kw)
	#3 (#1 AND #2)
	#4 (appointment based:ti,ab,kw OR med sync:ti,ab,kw)
	#5 (#3 OR #4) AND [2008–2022]/py
Cochrane	#1 (medication or prescription medications or prescriptions or refill or refills):ti,ab,kw
	#2 (synchronization or synchronized or alignment or aligns or aligning):ti,ab,kw
	#3 #1 AND #2
	#4 (“appointment based” OR (med AND sync):ti,ab,kw)
	#5 #3 or #4

Note: Non-systematic review through google search was performed using the term “medication synchronization” within years 2008 and 2022.

APPENDIX B

TABLE B1 Risk of bias assessment of included studies.

ROBINS-1: Risk of bias in non-randomized studies of interventions							
Study	Bias due to confounding	Bias of selection of participants into the study	Bias in classification of interventions	Bias due to deviation from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of reported result
Holdford 2013	Orange	Orange	Green	Green	Green	Yellow	Green
Doshi 2016	Yellow	Orange	Green	Green	Green	Yellow	Green
Andrews 2017	Orange	Orange	Green	Green	Green	Yellow	Green
Painter 2015	Orange	Orange	Green	Green	Green	Yellow	Green
Ghassemi 2018	Orange	Green	Green	Green	Green	Yellow	Green
Neuner 2019	Orange	Yellow	Green	Green	Green	Yellow	Green
Krumme 2018	Orange	Orange	Yellow	Green	Green	Yellow	Green
Doshi 2017	Orange	Orange	Green	Green	Green	Yellow	Green
Holdford 2015	Orange	Orange	Green	Green	Green	Yellow	Green
Bernard 2019	Yellow	Orange	Green	Green	Green	Yellow	Green
Barnes 2018	Orange	Orange	Yellow	Green	Green	Yellow	Green
Girdish 2017	Orange	Yellow	Green	Green	Green	Yellow	Green
Korn 2019	Yellow	Orange	Green	Green	Green	Yellow	Green
Singleton 2017	Orange	Orange	Green	Green	Green	Yellow	Green
Hinson 2017	Orange	Orange	Green	Green	Green	Yellow	Green
Dao 2018	Yellow	Orange	Green	Green	Green	Yellow	Green
Shoppe 2022	Orange	Orange	Green	Green	Green	Yellow	Green
Luder 2018	Yellow	Orange	Green	Green	Green	Yellow	Green
Patterson 2016	Orange	Yellow	Green	Green	Green	Orange	Green
Ariyo 2019	Yellow	Orange	Green	Green	Green	Yellow	Green
Renfro 2020	Orange	Orange	Green	Green	Green	Yellow	Green
Cheng 2022	Orange	Orange	Green	Green	Green	Yellow	Green
Witry 2019	Orange	Orange	Green	Green	Green	Yellow	Green
Butler 2015	Yellow	Orange	Green	Green	Green	Yellow	Green
Phi 2021	Orange	Orange	Green	Green	Green	Orange	Green
Fitzpatrick 2019	Orange	Green	Yellow	Green	Green	Yellow	Green
ROBINS-2: Risk of bias in randomized trials							
Study	Risk of bias arising from the randomization process	Risk of bias due to deviations from the intended interventions	Missing outcome data	Risk of bias in measurement outcome	Risk of bias in selection of reported result		
DiDonato 2014	Green	Orange	Green	Green	Green		

Note: Green = low risk of bias; Yellow = moderate risk of bias; Orange = serious risk of bias; Red = critical risk of bias.

APPENDIX C

TABLE C1 Characteristics of studies included in the review.

Authors	Type of study	Objective	Type of Med-Sync	Type of outcomes	Results
Holdford 2013	Quasi-experimental	To assess the impact of an ABMS program on medication adherence and persistence with chronic medications.	ABM	CL	Patients enrolled in the medication synchronization program ($n = 47-81$) had adherence rates of 66.1%–75.5% during 1 year versus 37.0% to 40.8% among control patients. Program patients had 3.4–6.1 times greater odds of adherence compared with control patients.
Doshi 2016	Quasi-experimental	Analyzed patients' adherence before and after participation in a pilot prescription synchronization program and compared changes to those found in a contemporaneous control group.	Only Refill Synchronization	CL	The mean PDC increased from 0.86 to 0.89 in the hypertension subgroup, 0.71 to 0.78 in lipid-lowering drugs, and 0.7 to 0.8 in the antidiabetic agent subgroup.
Andrews 2017	Quasi-experimental	To assess and compare adherence to chronic medications among adults participating in TMM, an appointment-based medication synchronization program, to patients receiving usual care.	ABM	CL, UT	During the 6-month post-period, PDC ≥ 0.80 was achieved by 73.53%, 80.41%, and 75.00% of usual care patients taking oral diabetes, RASA, and statin medications. The percentage of on-time prescription refills increased from 69.68% to 84.75% in patients with diabetes, 79.04% to 89.56% in the hypertension group, and 78.26% to 89.07% in the hyperlipidemic group.
Painter 2015	Retrospective cohort	The study measured the collective impact of ABMS on medication adherence and persistence rates across 82 independently owned pharmacies.	ABM	CL	Adherence as measured by PDC was significantly greater in the ABMS enrollees than in controls across all drug classes studied. Enrollees were 13% more adherent than controls during the study period.
Ghassemi 2018	Retrospective cohort	To compare antiretroviral adherence (measured as the proportion of days covered [PDC]) and change in viral load in insured, HIV-infected, adult outpatients enrolled and not enrolled in a medication synchronization program.	Only Refill Synchronization	CL	PDC in patients undergoing medication synchronization was significantly higher than in control patients: mean \pm SD $96 \pm 9\%$ versus $71 \pm 27\%$, respectively ($p < 0.0001$). The medication synchronization group was also more likely to be adherent to ART than the control group (odds ratio 10.67, 95% confidence interval 2.63–43.31).

TABLE C1 (Continued)

Authors	Type of study	Objective	Type of Med-Sync	Type of outcomes	Results
Neuner 2019	Retrospective cohort	This study investigated whether poor pharmacy synchronization of medication fills (requiring refills on different days) acts as a barrier to adherence.	Only Refill Synchronization	CL	Those in the third (odds ratio, 1.29; 95% confidence interval, 1.04–1.59) and fourth (most) medication number-adjusted synchronization quartiles (odds ratio, 1.49; 95% confidence interval, 1.19–1.86) were more likely to be adherent than those in the least. Multivariate model predictions showed that the proportion of patients who were adherent over 1 year varied from 68.9% in the least synchronized quartile to 76.6% in the most synchronized one.
Krumme 2018	Retrospective cohort	To evaluate the impact of two regional pharmacy-based medication synchronization programs on adherence to cardiovascular medications, cardiovascular clinical outcomes, and healthcare resource use for fee-for-service Medicare beneficiaries with hypertension, hyperlipidemia, or diabetes.	ABM	CL	The mean PDC for the control group of patients without a synchronization program was 0.84 compared to 0.87 for synchronized patients.
Doshi 2017	Retrospective cohort	Examined the association between synchronized medication refill schedules and adherence.	Only Refill Synchronization	CL	Mean PDC scores ranged from 0.02 higher for anti-hypertensives to 0.07 higher for antidepressants in the synchronized refill group relative to the control group ($p < 0.01$).
Holdford 2015	Retrospective cohort	Compare the impact of a community pharmacy chain's ABMS program on medication adherence and persistence of existing users of chronic medications with individuals who are not enrolled in the program.	ABM	CL	Mean PDC scores ranged from 0.73 to 0.91 for ABMS patients ($n = 205-716$) and from 0.57 to 0.71 for usual care depending on the medication class. Odds of adherence was 2.3–3.6 times greater with ABMS.
Bernard 2019	Retrospective cohort	To determine if patients enrolled in a medication synchronization program have improvements in proportion of days covered (PDC) score for 3 of the Centers for Medicare and Medicaid Services adherence metrics medication classes.	Unspecified	CL, UT	The largest PDC score increases for the entire study population were seen in all three sync groups (RASA, diabetes, and statin) with corresponding statistically significant PDC score increases of 1.6%, 4.8%, and 2.9%, compared with 0.4%, 0.5%, and 1.3% changes in the control groups.

(Continues)

TABLE C1 (Continued)

Authors	Type of study	Objective	Type of Med-Sync	Type of outcomes	Results
Barnes 2018	Retrospective cohort	To compare the effects of three different appointment-based model (ABM) designs on medication adherence and medication use outcomes controlling for patient and pharmacy characteristics.	ABM	CL, UT	All of the ABM designs significantly increased the number of fills after enrollment.
Girdish 2017	Retrospective cohort	To understand the impact of prescription synchronization, offered through the ScriptSync [®] program at CVS pharmacies nationwide, on adherence and reducing visits to the pharmacy.	Only Refill Synchronization	CL, UT	Exposed patients had a 7.5 percentage point adherence improvement (from 79.6% to 87.1%), compared with a 2.8 percentage point improvement among the unexposed (from 78.1% to 80.9%) for a benefit of 4.7 percentage points ($p < 0.0001$). The program resulted in 0.17 fewer visits per month ($p < 0.0001$).
Korn 2019	Retrospective cohort	The change in number of medications a patient was taking before enrollment versus after enrollment in the access program and potential health care savings.	Only Refill Synchronization	UT	Pharmacist consultation and reconciliation decreased the average number of medications from 12 to 10 medications per patient. This study suggests that the delivery of coordination of care services through medication reconciliation, medication synchronization, and home visits has a positive effect on health outcomes for patients who have undergone a recent transition of care.
Singleton 2017	Prospective pre-post	Pilot a telephone intervention for providing targeted adherence interventions to patients taking oral medicines for diabetes.	Only Refill Synchronization	CL	Medication synchronization may be associated with a greater increase in PDC over a 120-day post-intervention period compared to patients who did not participate in medication synchronization (82% vs. 75.5%). The difference was not significant.
Hinson 2017	Retrospective pre-post	Determine the impact of a comprehensive medication synchronization program in an independent community pharmacy by (1) evaluating changes in Electronic Quality Improvement Platform for Plans and Pharmacies (EQIPP) scores and (2) examining the change in monthly prescription volume.	ABM	CL	There was improvement in all targeted EQIPP scores. There was a 7% improvement in proportion of days covered (PDC) for cholesterol-reducing agents, a 9.5% improvement in PDC for oral glyceic agents, a 1.2% improvement in PDC for renin-angiotensin system antagonists, and a 1.8% reduction in the use of high-risk medications in the elderly. There was also an average increase in monthly prescription volume of 4.8%.

TABLE C1 (Continued)

Authors	Type of study	Objective	Type of Med-Sync	Type of outcomes	Results
Dao 2018	Retrospective pre-post	To evaluate the impact of implementing an ABMS program on pharmacy adherence measures for statins, ACEI/ARBs, and NIDM.	ABM	CL	All adherence measures showed statistically significant improvement in PDC percentage post-ABMS implementation, except for NIDM percentage in 6-month post-ABMS service.
Shope 2022	Retrospective pre-post study	To determine the impact of an adherence packaging and medication synchronization program on hospital visits for older people living independently in the community.	Medication synchronization, adherence packaging, home delivery	UT	Enrollment in the program was associated with fewer hospital visits but the difference was non-significant.
Luder 2018	Prospective cohort	To incorporate the assessment of vaccination status and administration of vaccines in an ABM and measure the impact on vaccinations administered and patient and pharmacist satisfaction with the appointment-based model.	ABM	UT, HU	The pharmacist vaccine assessment as part of the ABM program showed higher overall mean vaccinations per store compared with the control group during the project period (1810.71 ± 500.88 vs. 1455.09 ± 754.43; $p = 0.01$). Patients and pharmacists felt that the ABM program facilitated vaccine discussions.
Patterson 2016	Economic evaluation	To evaluate the cost-benefit of ABMS offered in community pharmacies for patients taking chronic medications to prevent negative outcomes associated with hyperlipidemia, hypertension, and diabetes.	ABM	UT	Medical savings per additional dollar spent on medications ranged from approximately \$1 to \$37 depending on the medication and medication class considered.
Ariyo 2019	Retrospective cross-sectional	To characterize medication therapy problems (MTPs) and vaccines recommended and administered by pharmacists during initial ABMS visits, in a community pharmacy setting.	ABM	CL	Thirty-seven MTPs were identified with no statistical difference between men and women ($p < 0.98$). Six hundred thirty-three vaccines were recommended, and 51 were administered.
Renfro 2020	Cross-sectional	The aims of this study were to (1) examine pharmacy characteristics associated with medication synchronization adoption and (2) examine whether medication synchronization is associated with pharmacy-level performance on select medication adherence and utilization measures.	Medication Synchronization	CL, UT	Pharmacies that adopted medication synchronization were more likely to have a clinical pharmacist on staff ($p = 0.019$). Medication synchronization adoption was not significantly associated with total medication adherence performance ($p = 0.371$).

(Continues)

TABLE C1 (Continued)

Authors	Type of study	Objective	Type of Med-Sync	Type of outcomes	Results
Cheng 2022	Retrospective cross- sectional	Identify ABM core component(s) that improve pharmacy-level medication adherence rates and evaluate what proportion of prescription volume synchronized affects medication adherence.	ABM	CL	All five core components of ABM showed significance for driving medication adherence in the chronic disease categories. When compared with synchronizing 0%–15%, synchronizing 31%–50% of a pharmacy's total prescription volume could increase medication adherence in every chronic disease category.
Witry 2019	Cross- sectional	To assess the feasibility of a combined medication synchronization and diabetes education program	Refill synchronization	CL, HU	There appeared to be a benefit to PDCs associated with medication synchronization, although most patients remained above the 80% threshold for being considered adherent. Participants also were satisfied with the medication synchronization intervention and would recommend the program.
Butler 2015	Cross- sectional survey	To assess participant satisfaction with a community pharmacy-based medication synchronization program.	Only Refill Synchronization	HU	Participants were highly satisfied with the Time My Meds (TMM) medication synchronization program. Participants' comments were generally positive, indicating that TMM was convenient and increased accountability.
Phi 2021	Cross- sectional	Evaluate the impact of a comprehensive medication adherence packaging service on patient medication-taking behaviors and patient-centered outcomes.	ABM	HU	This study found that 88% of patients in RxMAP service reported missing fewer doses and 76% reported they were more likely to take their medications on time.
Fitzpatrick 2019	Retrospective chart review	To describe the drug therapy problems (DTPs) identified for patients enrolled in an ABM for medication synchronization.	ABM	CL	ABM approach identified DTPs ($n = 334$). DTPs include the need for additional drug therapy (43.1%), inappropriate adherence (31.4%), unnecessary drug therapy (15.0%), and adverse drug reaction (9.6%).
DiDonato 2014	Randomized controlled trial	To examine the effect of a medication synchronization or education program on hypertensive health outcomes.	ABM	CL	Compared to the control group, there were no significant differences between control, medication synchronization, and education groups at final blood pressure analysis.

Abbreviations: ABM, appointment-based model; ABMS, appointment-based medication synchronization; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blockers; ART, antiretroviral therapy; CL, clinical outcomes; HIV, human immunodeficiency virus; HU, humanistic outcomes; NIDM, noninsulin diabetic medication; PDC, proportion of days covered; RASA, renin-angiotensin-system antagonist; TMM: Time My Meds; UT, utilization/economic outcomes.