POLICY

Prevalence, Effectiveness, and Characteristics of Pharmacy-Based Medication Synchronization Programs

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ABSTRACT

Objectives: The burden of visiting pharmacies to fill medications is a central contributor to nonadherence to maintenance medications. Recently, pharmacies have begun offering services that align prescription fill dates to allow patients to pick up all medications on a single visit. We evaluated the prevalence and structure of synchronization programs and evidence of their impact on adherence and clinical outcomes.

Study Design: Mixed-methods approach consisting of semi-structured interviews, data from surveillance activities, and a systematic literature review.

Methods: We conducted interviews with opinion leaders from nonprofit advocacy organizations and exemplary synchronization programs. Program prevalence was determined using data from regular surveillance efforts. A literature review included Medline, EMBASE, Google Scholar, and general Internet searches.

Results: Synchronization programs exist in approximately 10% of independent, 6% of stand-alone chain, and 11% of retail store pharmacies. The majority of programs include a monthly pharmacist appointment and reminder communication. Programs reported the importance of pharmacist buy-in, technology to track and recruit patients, links to other healthcare services, and flexible solutions for managing costs and communication preferences. Although existing peer-reviewed literature suggests that synchronization improves adherence, more evidence is needed to evaluate its impact on patient-centered outcomes.

Conclusions: As medication synchronization programs shift directions and compete for patients and payer resources, it will be more important than ever to rigorously evaluate their ability to improve clinical outcomes while also providing the growing number of patients managing multiple chronic conditions with the highest level of patient engagement and consumer choice.

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In the United States, chronic noncommunicable diseases are responsible for more than half a million deaths annually and more than $538 billion in direct medical costs.[1,2-4] Although medications are central to the effective management of these diseases, gaps in pharmaceutical care have been widely documented,[5] and are a major contributor to potentially avoidable morbidity, mortality, and health spending. Many factors undermine the ability of patients to adhere to their prescribed therapies,[6] and the burden of visiting pharmacies to fill and refill medications has recently been recognized as a central concern.[7-9]

Patients with chronic conditions must often manage medications prescribed by numerous physicians and may fill their prescriptions on many different days. For example, patients with cardiovascular disease make an average of 20 pharmacy visits annually, and the top decile make more than 43 visits.[8] This makes establishing a routine around medication filling challenging, especially when insurance restrictions frequently prohibit refilling until the supply from the prior prescription has been nearly exhausted. The resultant impact on adherence for patients whose prescriptions' fill dates are not aligned appears to be very large.[8,10-12]

To overcome this problem, pharmacies have begun to offer "medication synchronization" services that aim to simplify the refilling process by allowing patients to pick up all of their medications on a single visit. To accomplish this, patients receive partial supplies of their medications in order to align their subsequent refill dates. Medication synchronization programs—which in addition to prescription synchronization often include other pharmacy-based services, such as medication management counseling or vaccination—have attracted substantial and growing enthusiasm.[13] Initial estimates of their impact suggest that, depending on drug class, medication synchronization programs may improve adherence up to 6-fold.[14,15] However, to date, little is known about these programs, how they have

Take-Away Points

Medication synchronization is a novel delivery redesign in pharmacy care that has attracted growing enthusiasm; however, little is known about its impact on adherence and clinical outcomes.

- An estimated 8% of US pharmacies offer a medication synchronization program—a rate that nearly doubled from 2013 to 2014.
- Synchronization programs are based on 2 core models with additional features, including technology to track and recruit patients, links to other healthcare services, and flexible solutions for patients to manage medication costs and communication preferences.
- As programs expand, more attention will need to be devoted to care continuity and cost.

been implemented, who they serve, and what features appear to be associated with their success.

METHODS

We used a mixed-methods approach to determine how common synchronization programs were in 2013 and 2014, how many patients they impacted, how they are structured, and what aspects of their implementation and design appear to be associated with greater success.

Prevalence and Program Structure

To determine the prevalence, scope, and characteristics of existing programs, we conducted interviews with opinion leaders from the National Community Pharmacist Association (NCPA) and Pharmacy Quality Alliance, organizations that have been actively involved in monitoring, developing, and promoting medication synchronization programs. Three investigators conducted in-depth 60-minute telephone interviews, between January and March 2014. Interviewers used a written guide that contained a list of key thematic areas and kept written notes, which were reconciled after every interview. The interviews were semi-structured, with questions designed to elicit insight into the origins of synchronization programs, their current state, and future challenges. This study was approved by the Institutional Review Board at Brigham and Women's Hospital.

The prevalence of synchronization programs in chain and retail store pharmacies was determined through data collected from our opinion leaders who systematically survey program administrators biannually by e-mail or telephone. Programs report the number of stores with a synchronization program, the number of patients enrolled, and the projected estimates of patient enrollment, which enables leaders to reconcile new data with past projections. This surveillance approach captures information from an estimated 80% to 90% of chain (stand-alone pharmacies with 4 or more stores) and retail store pharmacies (pharmacies embedded in retail outlets, such as supermarkets) nationwide. Program prevalence in independent pharmacies (stand-alone pharmacies with fewer than 4 stores) was ascertained using official and self-reported data collected by NCPA through quarterly surveys to all affiliated pharmacies.

Impact on Adherence and Clinical Outcomes

To estimate the impact of existing synchronization programs on adherence and clinical outcomes, we conducted a systematic review of the peer-reviewed literature in November 2014 using Medline and EMBASE. We sought to identify studies reporting original data on the impact of medication synchronization programs on adherence to chronic disease medications and on clinical outcomes.

From the abstracts identified through medical subject headings (MESH) and keywords for medication synchronization (N = 376), 111 met our criteria for medication adherence, and of these, 14 were selected for full text review. We excluded studies that did not evaluate a medication synchronization program (n = 2), did not evaluate adherence (n = 3), or for which no results were reported (n = 7). Our final sample consisted of 2 peer-reviewed studies.[14,16] A review of reference lists of full text articles and personal archives to identify additional studies potentially missed by our search strategy did not yield additional results.

We also conducted Internet and Google Scholar searches using a variety of synonyms for "medication synchronization," "adherence," "persistence," and several cardiovascular conditions. This strategy yielded 3 articles evaluating the impact of synchronization on adherence,[17-19] 1 evaluating the impact on systolic blood pressure,[20] and 1 evaluating both adherence and cardiovascular biomarkers.[21] To generate as complete a summary of the synchronization landscape as possible, we contacted the authors of peer-reviewed studies that did not present empirical results to obtain unpublished results. Two authors (AAK, DLI) conducted the systematic search and extracted data on study population, characteristics, results, and study limitations from each included article using standardized protocol and reporting forms.

Key Program Features and Innovations

To identify key features of synchronization programs, we asked our opinion leaders to nominate exemplary synchronization programs run by independent, chain, and retail store pharmacies. This process generated a consistent list of

7 exemplars. With 1 program declining to participate, our final list included 2 independent, 3 chain, and 1 retail store program.

For each nominated program, we conducted an interview with individuals who run or were involved in the program's creation. As with opinion leader interviews, 3 investigators conducted telephone interviews lasting 30 minutes each, between April and October 2014, and reconciled written notes after every interview. Each interview began by describing the study objectives and design, and obtaining the consent of the interviewee(s) to have their perspectives included in our analysis. Interviews were guided by semi-structured questions about how standard programmatic features are implemented and program elements developed to maintain program stability, growth, and patient satisfaction. We continued our interviews until we believed we had achieved a broad array of perspectives, which we assessed by identifying common themes across responses at the conclusion of every new interview.

Table 1. Medication Synchronization Prevalence

Characteristic	Pharmacy Type		
	Independent	Chain	Supermarket and Mass Merchant Retail Store
Pharmacies, N[a]	20,996	22,437	17,658
Number of businesses with a medication synchronization program, 2014	2200	8	14
Number of pharmacies with a medication synchronization program, 2014	2200	1396	1938
Total patient population synched, 2014	83,000	88,126	266,974
Number of synched patients per business, 2014: mean (SD)	38 (N/A)	12,589 (16,812)	19,070 (57,445)
Number of businesses with a medication synchronization program, 2013	1250	11	13
Number of pharmacies with a medication synchronization program, 2013	1250	463	1611
Total patient population synched, 2013	49,000	59,528	16,080
Number of synched patients per business, 2013: mean (SD)	39 (N/A)	5953 (11,432)	1237 (2005)

N/A indicates not available.
[a]Source: National Association of Chain Drug Stores 2012, evaluated December 2014.

RESULTS

Prevalence and Structure of Medication Synchronization Programs

Medication synchronization programs were offered by approximately 10% of independent, 6% of chain, and 11% of retail pharmacy stores in 2014 (Table 1). Compared with chains, retail store pharmacies reported having 50% more participating pharmacies (1938 vs 1396, respectively). Median program enrollment was 4843 and 475 patients for chain and retail stores with a program, respectively.

All chain and retail store pharmacies with a synchronization program, which collectively have more than 350,000 patients enrolled,[13] follow a model initially developed by Abrams and Clark independent pharmacy, which was formalized and expanded by the NCPA and the American Pharmacists Association.[13,22] The key components of this approach, called the appointment-based model (ABM), are the alignment of prescription fill dates, a monthly call or text message to remind patients to pick up their medications, and a scheduled monthly appointment with comprehensive medication review or other medication therapy management.[23]

A second standardized program, which evolved from the original ABM framework and is branded specifically for independent pharmacies, is the Simplify My Meds (SMM) program. Developed by the NCPA as a resource package for independent pharmacists, the program is characterized by prescription synchronization and regular reminder calls, with less emphasis on monthly appointments.[24] Over 2200 independent pharmacies in the United States have enrolled approximately 83,000 patients into programs using SMM.

Impact of Existing Programs on Adherence and Clinical Outcomes

The results of our systematic review of the impact of medication synchronization programs on adherence and clinical outcomes are presented in Tables 2 and 3. All studies except for 1 were observational and used either a control group or a pre-/post analysis with time as a control. Four studies were full-length reports or articles,[14,17,20,21] 1 was a published abstract,[16] and 2 were conference posters.[18,19] Studies also ranged in size, from pilots of fewer than 10 patients to a retrospective analysis of over 20,000 patients. Three studies evaluated the University of Mississippi RxSync program.[16,18,19]

All studies evaluating an adherence outcome measured adherence to antihypertensive, hyperlipidemic, and/or oral hypoglycemic therapy. The 2 peer-reviewed articles were the only ones to conduct statistical testing of results, both finding significantly higher adherence in synched patients compared with usual care, with up to 6-fold greater odds of patients being fully adherent (Table 3).[14,19] Other

Table 2. Systematic Review Results

Reference	N	Study Population	Study Design	Primary Outcome
Adherence				
Holdford (2013)[14]	~23,000	Patients taking 1 of 6 classes of chronic disease medications and filling prescriptions at Thrifty White pharmacies, 2011-2012	Retrospective matched cohort, with matching based on drug class, age, gender, region, and start date	Optimal adherence (proportion of days covered ≥80%)
Datar (2013)[16]	Not stated	Patients enrolled in Mississippi Medicaid and taking statins, antihypertensives, or oral hypoglycemics, 2008-2011	Retrospective matched cohort, with matching based on age, gender, and race	Mean proportion of days covered at 6 months
Holdford (2011)[17]	1704	Patients enrolled in "Patient Centric Model" and taking 1 of 8 classes of chronic disease medications, 2008-2010	Pre- vs post analysis, no control group	Difference in medication nonpersistence (pre-baseline vs months 8-12)
Banahan (2011 presentation)[18]	221	Patients enrolled in RxSync Service, 2007-2010	Pre- vs post analysis, no control group	Mean medication possession ratio (pre- vs post intervention)
Datar (2013 presentation)[19]	~200	Patients enrolled in RxSync Service and taking statins, antihypertensives, or oral hypoglycemics, 2008-2011	Retrospective matched cohort, with matching based on age, gender, and drug class	Optimal adherence (proportion of days covered ≥80%)
Schmidt (2010)[20]	9	Patients taking antihyperlipidemics, antihypertensives, oral hypoglycemics and filling at a high-volume pharmacy in Oregon	Pre- vs post analysis, no control group	Mean medication possession ratio (pre-baseline vs month 4)
Cardiovascular Outcome				
DiDonato (2014)[21]	302	Hypertensive patients filling at community pharmacy chain in Missouri	Randomized control trial	Change in average systolic blood pressure among 2 intervention and 1 control groups
Schmidt (2010)[20]	2	Patients taking cholesterol, antihypertensive, or oral hypoglycemic medications and filling at a high-volume pharmacy in Oregon	Pre- vs post analysis, no control group	Change in average blood glucose and triglyceride levels (mg/dL) (pre-baseline vs month 4)

studies demonstrated improved adherence or persistence due to synchronization with different lengths of follow-up; however, the small sample size suggests some are underpowered to detect significant differences.[17,25,26] More information on study quality and limitations is presented in the eAppendix (available at **www.ajmc.com**).

Key Program Features and Innovations

Characteristics of the nominated exemplar programs are summarized in Table 4; 5 of these programs followed the ABM model, and 1 the SMM model. Four programs reported targeting patients taking 2 or more medications; 1 targets all patients regardless of medication count; and another only targets patients on an ad hoc basis, such as individuals who take many medications, seniors, and family caregivers. Exemplars identified 5 innovative features deemed critical to their program growth and success:

1. Technology to track patients and identify opportunities. Synchronization on a smaller scale involves patient binders and a "pen-and-paper" approach to fill alignment. More recently, chain and retail pharmacies have implemented automated mechanisms that streamline targeting and management of their synchronized patient populations. One exemplar views the transition from live to automated reminder calls as a critical step in its plans to expand its program more than 20-fold. Technology has also facilitated patient engagement, with regular reminder messaging acting as a consistent link with healthcare providers.

2. Pharmacist consultation to reinforce adherence and link to other services. Exemplars cited the monthly pharmacist appointment as an important opportunity to direct patients to other healthcare services available in the pharmacy, including behavioral counseling and medication therapy management services. One exemplar plans to provide periodic glycated hemoglobin testing to program enrollees with diabetes, while another has embedded its pilot synchronization program into an existing compliance program in which pharmacists communicate adherence scores to patients. Several exemplars use pre-visit calls and monthly appointments to provide vaccination reminders and introductions to smoking cessation counseling.

3. Care integration. Exemplars from independent pharmacies noted the importance of integration with a patient's primary care physician. One exemplar contacts hospitals for

Table 3. Impact of Medication Synchronization on Adherence and Cardiovascular Outcomes

Studies With a Control Group					
Reference	**Outcome**	**Exposure**	**Intervention**	**Control**	***P* (95% CI)**
Holdford (2013)[14]	Odds ratio for optimal adherence	ACE inhibitors/ARBs	6.1	1.0 (ref)	(4.2-9.0)
		Beta-blockers	4.7	1.0 (ref)	(3.1-7.1)
		Calcium-channel blockers	3.8	1.0 (ref)	(2.2-6.7)
		Thiazide diuretics	3.4	1.0 (ref)	(1.6-7.5)
		Metformin	4.8	1.0 (ref)	(2.0-11.5)
		Statins	5.8	1.0 (ref)	(4.0-8.4)
Datar (2013)[16]	Mean proportion of days covered at 6 months	Statins, antihypertensives, oral hypoglycemics	87.9%	81.2%	*P* = .01
Datar (2013 presentation)[19]	Percent of patients with optimal adherence	Statins, antihypertensives, oral hypoglycemics	74.2%	65.5%	–
DiDonato (2014)[21]	Change in systolic blood pressure, baseline vs month 4	Antihypertensives	4 mm Hg	9 mm Hg	–
Studies With Time as a Control					
Reference	**Outcome**	**Exposure**	**Pre-Baseline**	**Post Baseline**	***P* (95% CI)**
Holdford (2011)[17]	Difference in medication persistence (pre-baseline vs months 8-12)	ACE inhibitors/ARBs	67%	76%	–
		Beta-blockers	64%	76%	–
		Calcium-channel blockers	63%	75%	–
		Thiazide diuretics	60%	70%	–
		Metformin	60%	75%	–
		Statins	63%	76%	–
		Sulfonylureas	63%	69%	–
		SSRI/SNRI	62%	75%	–
Banahan (2011 presentation)[18]	Average medication possession ratio	All chronic disease medications	84%	87%	–
Schmidt (2010)[20]	Average medication possession ratio (pre-baseline vs month 4)	Antihyperlipidemics, antihypertensives, oral hypoglycemics	88.5%	105%	–
Schmidt (2010)[20]	Average laboratory value (pre-baseline vs month 4)	Blood glucose	207 mg/dL	186 mg/dL	–
		Triglyceride	354 mg/dL	183 mg/dL	–

ACE indicates angiotensin converting enzyme; ARB, angiotensin II receptor blocker; SNRI, serotonin-norepinephrine reuptake inhibitor; ref, reference; SSRI, selective serotonin reuptake inhibitor.

discharge orders to enable medication reconciliation with the physician, while another employs staff whose role is to relay acute health changes to a clinical staff member and follow up with the patient, caregiver, or physician, as needed. Both exemplars reported screening for therapeutic deficiencies and communicating these to the patient's primary care provider at program start and throughout follow-up.

4. Flexible solutions for patients. Program flexibility and patient autonomy have been important in overcoming barriers to adoption and use. Across all programs, patients can select their synchronization start date and the timing of their refills, which allows them to manage co-payments around paycheck schedules or other budgetary constraints. Pharmacists across several programs can adjust fill dates to coincide with a paycheck or anchor the synchronization to the most expensive co-payment and supply remaining medications at either a reduced cost or free of charge.

Programs have also adjusted patient outreach approaches in response to some patients who dislike receiving automated calls, as seen in one exemplar program that calls all patients with caregivers who pick up their prescriptions. Other exemplars allow patients to opt out of text reminders and to easily be transferred to a live pharmacist during an automated call.

5. Pharmacist buy-in. Exemplars reported instances where pharmacist resistance to synchronization programs resulted in worse performance and slower program rollouts, highlighting the need for sensitivity to pharmacist workforce culture. Several approaches to improving pharmacist buy-in have been implemented, including tailored

Table 4. Exemplar Synchronization Program Characteristics

Characteristic	Exemplar 1	Exemplar 2	Exemplar 3	Exemplar 4	Exemplar 5	Exemplar 6
Pharmacy type	Independent	Independent	Small chain	Small chain	Large chain	Large chain
US region	West	South	West	Midwest	Nationwide	Nationwide
Program model	ABM	ABM with SMM framework	ABM	ABM	ABM	ABM
Percent of pharmacies with synchronization program[a]	100%	100%	100%	100%	4%	7%
Number of synched patients[a]	350	1300	4000	50,000	3400	2800
Unique solutions	▪ Screen for hospitalizations and changes in orders ▪Screen for therapy failures and communicate medication issues or discontinuation to patients' physicians	▪ Offer option to synchronize refills across family members ▪ Medication delivery option for ill patients with chronic conditions ▪ Obtain discharge plans from nursing home or hospital for transitioning patients	▪Target Medicare Part D patients for enrollment ▪ Offer adherence packaging option ▪ Conduct calls to patients at convenient times ▪ Offer A1C testing for patients with diabetes	▪ Utilize independent, central fill site to simplify work flow ▪ Utilize patient care center that conducts routine, monthly calls ▪ Notify personal physician upon program enrollment	▪ Utilize technological flagging system that helps pharmacists identify and enroll eligible patients ▪ Have synchronization program embedded in proprietary program	▪ Offer phone communication option for patients with caretakers or those physically unable to attend monthly appointments ▪ Have flexible options for partial fills

A1C indicates glycated hemoglobin; ABM, appointment-based model; PCP, primary care physician; SMM, Simplify My Meds.
[a]Rounded number.

training tools and educational materials emphasizing to pharmacists the benefits of practicing "at the top of their license" and having more sustained patient interactions over time, as well as the use of small pilots prior to full roll-out to identify pain points, solicit pharmacist feedback, and refine training materials.

DISCUSSION

Medication synchronization is a novel delivery redesign in pharmacy care that directly addresses complexity in the prescription filling and refilling process, a burden that disproportionately affects the growing number of patients who manage multiple chronic conditions. An estimated 8% of all pharmacies across the country offer a medication synchronization program—a rate that nearly doubled from 2013 to 2014. Today, medication synchronization programs are estimated to have over 1.5 million patients enrolled.

Although synchronization programs have proliferated in the last 2 years, evidence regarding improvements in patient-centered outcomes remains sparse. Results from a recent follow-up study by Holdford et al to their original study[15] suggest that synchronization leads to meaningful improvements in adherence. However, none of the studies we identified through an extensive systematic review process robustly accounted for the fact that patients choosing to enroll in a synchronization program may be very measurably different from the general population, and that enrollment may lead to behavior changes that are independent of the program mechanism itself. Moreover, the short length of follow-up and small sample sizes in the studies evaluating cardiovascular biomarkers may have obscured our ability to see an impact on clinical outcomes. Robust research is needed to evaluate the impact of synchronization on clinically relevant outcomes and to compare effectiveness across programmatic features. Further, synchronization programs may confer additional benefits to patients that have not been measured by existing studies, such as improvements in patient safety and increased patient engagement through routine monthly appointments with pharmacists.

All existing synchronization programs are based on 2 standard program models; however, several additional features have contributed to the success and growth of these programs, including technology to track and recruit patients, links to other healthcare services, and flexible solutions for patients to manage medication costs and communication preferences. Interestingly, the exemplar programs we interviewed generally did not report relying on integration with care providers, seeing the monthly pharmacist appointment as sufficient to track changes in

therapy regimens over time. It is not clear whether such a minimal level of care integration will serve the longer-term health of patients. Already, several studies have demonstrated the benefit of physician–pharmacist collaborations in chronic disease management and that alternative care models, such as embedded pharmacists in patient-centered medical homes, may provide better clinical outcomes at lower cost to payers.[27,28]

Meanwhile, recent studies of retail clinics found in many pharmacies suggest that the use of such clinics for the management of chronic conditions may disrupt continuity of care.[29] Finally, more consideration will be needed regarding critically ill patients, particularly those with mental disabilities and those who rely on caregivers to pick up their medications.

Longer fills of chronic medications have become an important feature of pharmacy benefit design, with many plans requiring that such medications be filled by mail. To the extent that patients are restricted by mail order requirements, synchronization programs available at retail pharmacies may result in incomplete synchronization for such patients. Development of an analogous or complementary mail order program may be able to respond to these gaps in synchronization; however, they may also add complexity if patients are in 2 different synchronization programs simultaneously. A larger body of evidence—one that engages in comparative evaluations of medication synchronization program elements—will go a long way in demonstrating which interventions are most effective and transportable to other populations.

Exemplar programs did not report program cost as a major obstacle to growth, nor did they express concern over lost revenue due to reduced foot traffic in pharmacies. Program cost may not be an immediate concern if some program costs are recouped in the increased number of prescriptions that are filled by enrolled patients. Moreover, among chain pharmacies, medication synchronization is part of a larger rebranding strategy. By linking to the increasing number of healthcare services offered at many pharmacies, synchronization programs are expected to generate increased revenue.

A significant business strategy that several exemplar programs acknowledged is the use of synchronization programs to build relationships with healthcare payers. In so-called "narrow networks," payers contract with pharmacies to generate preferred access to their patient populations in exchange for lower reimbursement rates.[30] Synchronization programs have already attracted potential Medicare Part C and D sponsors by demonstrating improved adherence Star Ratings results, which for Part C sponsors are tied to increased reimbursement from CMS.[31]

Such agreements between payers and pharmacies may translate into less choice for patients regarding programs and whether to enroll at all. Conversely, if programs target specific groups of patients, such as those with higher costs, other patients who stand to benefit from synchronization may be excluded. Other shifts in program features aimed at reducing payer healthcare expenditures, such as automatic refilling or at mail refills only, may perversely result in reduced adherence if patients perceive these changes as restrictive or inconvenient.

A final area of change already underway is a legislative push to compel payers to allow partial co-payments for short fills of medications. A Medicare 2014 call letter requires sponsors to offer partial co-payments, with the specific mention of medication synchronization.[32] Following CMS' lead, legislative bills have been introduced in 13 states and approved in 3 that require payers to allow partial co-payments for partial fills. Detractors of legislation argue that allowing partial fills would result in a costly administrative burden for pharmacy benefits managers and would raise healthcare costs.

Limitations

As the landscape of these programs is rapidly evolving, our methodology may underreport the current number of programs and enrolled patients, as well as the wide array of program elements being implemented. Although we relied on impartial expert sources for this information, no formal nationwide estimation has taken place. Nonetheless, we believe that our approach accurately captures predominant trends while minimizing methodological bias. Additionally, because our results were based on experts speaking on behalf of exemplar programs, our findings may not be generalizable to all synchronization programs. We attempted to minimize such bias by forming a priori hypotheses about programmatic features and by not distributing questions to participants ahead of the interview.

CONCLUSIONS

As synchronization programs take on new directions and compete for patients and payer resources, it will be more important than ever to rigorously evaluate their ability to improve clinical outcomes while also providing the growing number of patients managing multiple chronic conditions with the highest level of patient engagement and consumer choice.

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eAppendix. Systematic Review Study Limitations

Reference	Study Limitations
Holdford DA, Inocencio TJ. Adherence and persistence associated with an appointment-based medication synchronization program. *J Am Pharm Assoc (2003)*. 2013;53(6):576-583. doi:10.1331/JAPhA.2013.13082.	▪ Potential residual confounding after matching ▪ Length of follow-up not stated
Datar M, Banahan BF, Hardwick S, Clark J. Analysis of the impact of prescription synchronization on adherence among Medicaid beneficiaries. *Value Health*. 2013;16:A1-A298.	▪ Potential residual confounding after matching ▪ No baseline characteristics reported, generalizability unknown
Holdford D, Inocencio T. Patient Centric Model: Pilot data analysis report. Prepared for the Alliance for Patient Medication Safety. American Pharmacists Association website. http://www.aphafoundation.org/sites/default/files/ckeditor/files/NASPA%20Report%204-08-2011%20Final%20Reports.pdf. Published April 2011. Accessed December 1, 2014.	▪ No statistical testing ▪ No baseline characteristics reported, generalizability unknown ▪ Does not account for secular time trends (lack of control group)
Banahan BF, Bynum LA, Holmes ER. Implementing a new prescription synchronization program that positively influences patient medication compliance. Presented at the: American Pharmacists Association Annual Meeting and Expo; March 25-28, 2011; Seattle, WA.	▪ No statistical testing ▪ No baseline characteristics reported, generalizability unknown ▪ Does not account for secular time trends (lack of control group) ▪ Length of follow-up not stated
Datar M, Banahan BF, Hardwick S, Clark J. Analysis of the impact of prescription synchronization on adherence among medicaid beneficiaries. Presented at the: Annual International Meeting of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR); May 18-22, 2013; New Orleans, LA. http://pharmacy.olemiss.edu/cpmm/wp-content/uploads/sites/18/2014/03/datar_and_banahan_outcomes_of.pdf. Accessed April 12, 2013.	▪ Potential residual confounding after matching ▪ No statistical testing ▪ No baseline characteristics reported, generalizability unknown ▪ Length of follow-up not stated
Schmidt T, Ramirez S, Davis J, Henson J, McLeod R. Evaluating prescription synchronization and medication management in a community pharmacy [unpublished]. Portland, OR; Fred Meyer-Oregon State University; 2010.	▪ Underpowered for inference ▪ No statistical testing ▪ No baseline characteristics reported, generalizability unknown
DiDonato KL, Vetter KR, Liu Y, May JR, Hartwig DM. Examining the effect of a medication synchronization or an education program on health outcomes of hypertensive patients in a community pharmacy setting. *Inov Pharm*. 2014;5(3): article 175.	▪ Incomplete balance of confounders after randomization ▪ Potential contamination due to no blinding