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REVIEW

The impact of patient support programs on adherence, clinical, humanistic, and economic patient outcomes: a targeted systematic review

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Background: Patient support programs (PSPs), including medication management and counseling, have the potential to improve care in chronic disease states with complex therapies. Little is known about the program's effects on improving clinical, adherence, humanistic, and cost outcomes.

Purpose: To conduct a targeted review describing medical conditions in which PSPs have been implemented; support delivery components (eg, face-to-face, phone, mail, and internet); and outcomes associated with implementation.

Data sources: MEDLINE – 10 years through March 2015 with supplemental handsearching of reference lists.

Study selection: English-language trials and observational studies of PSPs providing at minimum, counseling for medication management, measurement of ≥1 clinical outcome, and a 3-month follow-up period during which outcomes were measured.

Data extraction: Program characteristics and related clinical, adherence, humanistic, and cost outcomes were abstracted. Study quality and the overall strength of evidence were reviewed using standard criteria.

Data synthesis: Of 2,239 citations, 64 studies met inclusion criteria. All targeted chronic disease processes and the majority (48 [75%]) of programs offered in-clinic, face-to-face support. All but 9 (14.1%) were overseen by allied health care professionals (eg, nurses, pharmacists, para-professionals). Forty-one (64.1%) reported at least one significantly positive clinical outcome. The most frequent clinical outcome impacted was adherence, where 27 of 41 (66%) reported a positive outcome. Of 42 studies measuring humanistic outcomes (eg, quality of life, functional status), 27 (64%) reported significantly positive outcomes. Only 15 (23.4%) programs reported cost or utilization-related outcomes, and, of these, 12 reported positive impacts.

Conclusion: The preponderance of evidence suggests a positive impact of PSPs on adherence, clinical and humanistic outcomes. Although less often measured, health care utilization and costs are also reduced following PSP implementation. Further research is needed to better quantify which support programs, delivery methods, and components offer the greatest value for any particular medical condition.

Keywords: patient support services, patient assistance programs, medication management, specialty pharmacy, mediation adherence

Introduction

Chronic disease in the United States (US) accounts for a large proportion of health care expenditures. In the past 5 years, chronic disease has been responsible for over 75% of all health care-related costs,[1,2] and it is projected by 2020, that an additional 16 million US

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patients will be diagnosed with a chronic condition.[3] Chronic disease frequently requires multiple long-term medications and/or complex therapies. Particularly in the elderly, patients with chronic illnesses require long-term treatment to prevent disease progression, complications, and disability.[4] Patients with chronic illness often exhibit lower than recommended adherence to medications. In the US, approximately 50% of chronically treated patients do not adhere to their prescription medications, and many lack understanding of the importance of adherence and self-care.[5–7] Poor adherence to medication is significant and can lead to increased complications of disease, reduced quality of life, and increased overall health care costs related to complications.[1]

Self-management support programs are designed to provide patient education to support self-management behavior. These programs have demonstrated improved outcomes in a wide variety of diseases[8–12] through individual and group support[13] and multidisciplinary health care team coaching.[14] Patient support programs (PSPs) are enhanced self-management support programs that include interventions such as individualized medication counseling, training, support, and virtual reminders to improve medication-taking behavior. The underlying objective is to help patients better manage their disease and complex medication regimens, improve medication adherence, and reduce complications and related costs.

Despite the growing availability of PSPs, evidence on outcomes is not well understood. Specifically, there is insufficient understanding of PSPs' impact on clinical, adherence, humanistic, and economic outcomes. The objective of this targeted review is to answer the following questions: 1) in which disease processes have PSPs been implemented and published; 2) what components of support are encompassed within programs; and 3) what outcomes are impacted and measured related to PSPs (ie, adherence, clinical, humanistic, economic/utilization)?

Methods

The literature was systematically searched for studies describing PSPs implemented for chronic disease therapy reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement for reviews. PSPs were defined as interventions provided to patients with chronic disease requiring chronic and or complex medication therapy to manage symptoms and/or to control disease progression. Specifically, we targeted programs that included a medication counseling or management component incorporated into the interventions. Databases searched were PubMed/Medline and Web of Science using the terms ("patient support program" or "patient assistance program" or "medication management" or "disease therapy management" or "medication" or "drug therapy") and ("counseling" or "telemedicine" or "telehealth" or "health communication" or "health promotion" or "follow-up" or "reminder" or "reinforcement" or "supportive care") and ("face-to-face" or "in-person" or "home" or "internet" or "phone" or "telephone"). The search timeframe was 10 years, spanning from March 10, 2005 through March 10, 2015. Initial search results were deduplicated; titles and abstracts were screened independently for relevance by two reviewers with a third acting as adjudicator for discrepancies.

Included studies met the following criteria: 1) the intervention described included active medication counseling consisting of at least two live contacts for a specific chronic disease; 2) the study population consisted of adult patients; 3) the publication reported at least one clinical outcome that allowed a comparison between those receiving the intervention and a control group (derived from either randomized or nonrandomized controlled trials (non-RCTs), as well as pre- and post-implementation study designs); and 4) the follow-up period was at least 3 months. Studies evaluating programs that included interventions limited to medication refill reminders and publications not available in full-text or not in English were excluded. Self-described pilot studies and those with stated limitations of inadequate power or sample size were also excluded. Full-text articles were reviewed against these criteria. Reference lists of included studies and relevant review articles were handsearched for additional manuscripts meeting inclusion criteria.

Data abstraction

Data were abstracted from full text manuscripts by two individuals reviewing each manuscript, with a third acting as adjudicator for discrepancies. Abstracted data included disease states in which programs were implemented with related treatments and medications; components of implemented support interventions, including method of delivery (eg, face-to-face either in-clinic, in-pharmacy, or in home, by phone, via the Internet); implementing organization (eg, provider, payer, or other [eg, pharmacy benefit manager {PBM}]); background of the staff delivering support (eg, pharmacist, nurse, physician); funding source (eg, public/governmental, for-profit entities including insurers, PBM, pharmaceutical industry); and outcomes measured resulting from interventions (eg, clinical, adherence, humanistic, and economic). Evidence quality was examined in two ways. PSP evaluation studies using a randomized or cluster-RCT methodology were deemed the highest quality. Quasi-experimental, prospective observational cohort studies including single

arm pre- and poststudies were defined as medium quality, and retrospective cohort studies as lower quality. Quality was also assessed using a checklist for identification of bias risk adapted from the Cochrane Collaboration.[15] This included selection bias (systematic differences between baseline characteristics of the groups that are compared), attrition bias (systematic differences between groups in withdrawals from a study), performance bias (systematic differences between groups in the care that is provided, or in exposure to factors other than the interventions of interest), and reporting bias (systematic differences between reported and unreported findings). Each classification was marked as having a high, unclear, or low risk of bias. Studies were also evaluated for other sources of bias and were reported in a separate category from the classification biases. It was only determined as high risk if a bias was present (low risk for no presence of a bias).

Analysis

The data were analyzed and abstracted descriptively to understand the types of programs and related outcomes. The program-related clinical, adherence, humanistic, and health care cost outcomes were characterized as either positive – results indicate statistically significant for all primary and secondary end points, mixed – results indicate both met and failed end points, negative – no significant differences in any measured end point, and unclear – results not adequately described to determine program impact.

Results

Program composition

Of the 2,239 records reviewed, 64 were included in this review (Figure 1). Of programs' geographic distribution, 22 (34.3%) were implemented in the US, six (9.4%) in sub-Saharan Africa, five (7.8%) in the UK, three each

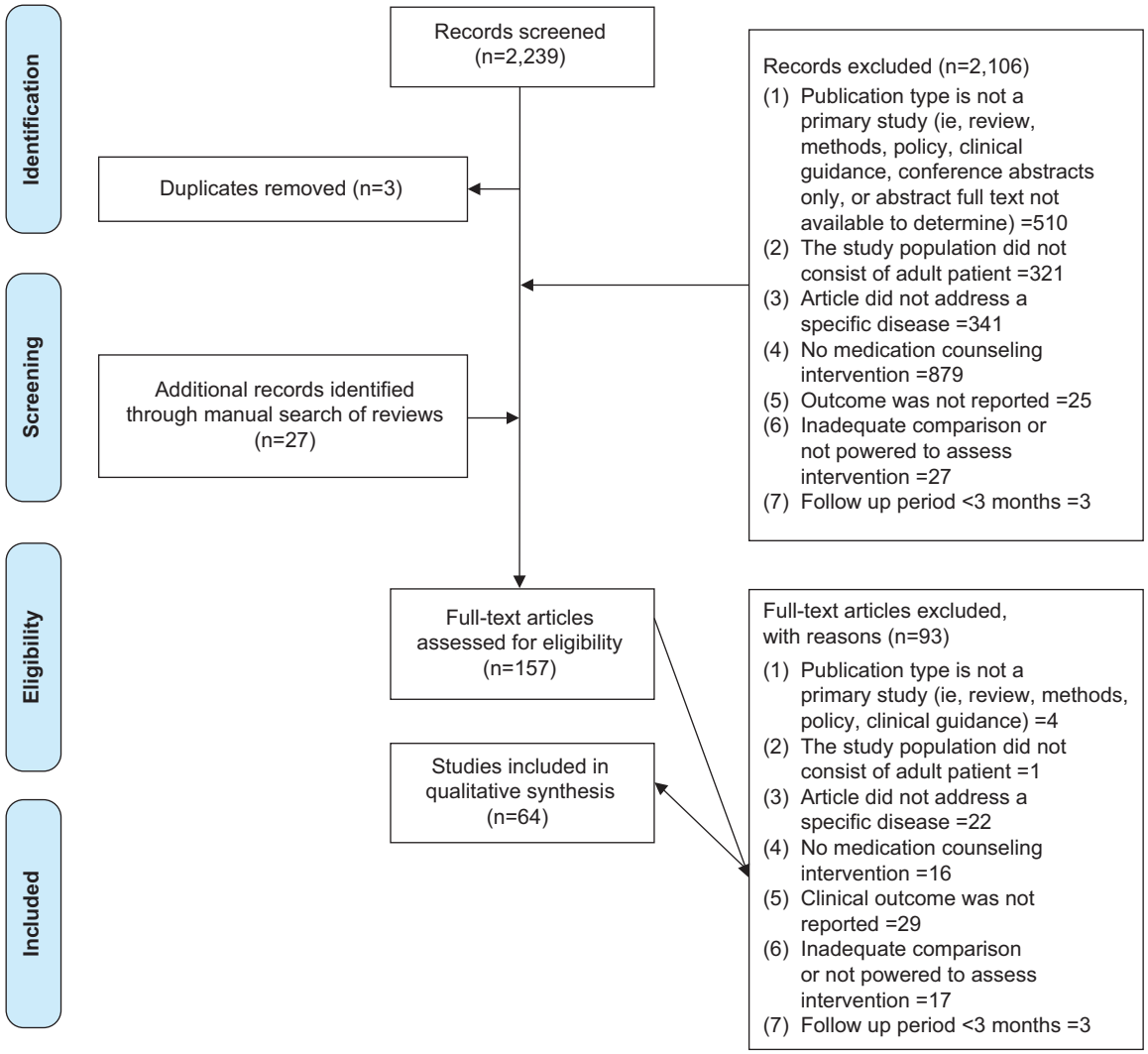

Figure 1 PRISMA diagram.
Abbreviation: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

(4.7%) in Canada, Germany, People's Republic of China, Spain, Taiwan, the Netherlands, and the Middle East, and two (3.1%) in India and Italy. Australia, Malaysia, Poland, Portugal, Thailand, and the Dominican Republic contributed one study each.

The most frequently targeted disease states for PSPs were for type 2 diabetes mellitus with 12 (18.8%) programs cited, followed by 11 (17.2%) for human immunodeficiency virus (HIV), with most programs evaluated via RCTs (Table 1). The vast majority (59 [92%]) of programs were developed and implemented by health care providers (92.2%), with the remainder created by insurers or specialty pharmacy providers, and one European Union governmental entity (Trans-European Network). Twenty-seven (42%) of the programs were specifically focused on recruiting and supporting patients receiving a specific drug or class of drugs for their disease (eg, highly active retroviral therapy in HIV, long-acting β-agonists in asthma, immunosuppressants/immunomodulatory in posttransplantation, anti-tumor necrosis factors in rheumatoid arthritis [RA]). The remainder were disease-focused with nonspecific medication counseling across all therapeutic classes prescribed for that condition (eg, congestive heart failure, metabolic syndrome). Fifty-four of the 64 included studies reported a source of funding. Seventeen studies (31%) were funded by the pharmaceutical industry or a PBM, 17 studies (31%) were funded by the government, and 20 studies (37%) were privately funded.

Table 1 Program and evaluation characteristics

Characteristics	N (%)
Disease states	
Type 2 diabetes mellitus/metabolic syndrome	12 (18.8)
HIV	11 (17.2)
Cardiovascular disease/CHF	10 (15.6)
Hypertension	8 (12.5)
Dyslipidemia/coronary risk reduction	5 (7.8)
Asthma/COPD	4 (6.3)
Osteoporosis	3 (4.7)
Renal transplant/failure	3 (4.7)
Rheumatoid arthritis	2 (3.1)
Multiple sclerosis	2 (3.1)
Cancer	1 (1.6)
Cerebral vascular disease	1 (1.6)
Glaucoma	1 (1.6)
Parkinson's disease	1 (1.6)
Study design	
Randomized controlled trial[a]	46 (71.9)
Prospective cohort (with controls)	8 (12.5)
Retrospective cohort (with controls)	7 (10.9)
Quasi-experimental[b]	4 (6.3)

Notes: [a]Includes cluster RCT and pragmatic trials, [b]pre–post design (2), waitlist design with control crossover (1), nonrandomized controlled trial (1).
Abbreviations: HIV, human immunodeficiency virus; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; RCT, randomized controlled trial.

In terms of program components, the majority (48 [75%]) of programs offered in-clinic service including face-to-face support with a health care provider. Thirty-five (54.7%) incorporated phone support, and 9 (14.0%) provided in-home support. Ten (15.6%) incorporated mailed or emailed reminders and information. Six programs (18.2%) included only phone support. Three (4.7%) included in-pharmacy consultations. Programs were administered by a variety of disciplines, with 29 (46.7%) overseen by pharmacists, 20 (31%) managed by nurses, 9 (13.8%) by physicians, and 8 (12.5%) by paraprofessionals such as health educators, trained counselors, community health workers, and patient advocates, with the remainder delivered using multidisciplinary teams (Table 2).

Overall program outcomes

All included studies measured at least one clinical end point in program evaluation. Of these, 43 (67.2%) also measured a humanistic outcome, 41 (64.1%) measured adherence, and 15 (23.4%) measured an economic/utilization outcome, including health care utilization such as prevention of hospitalization and costs to provide care. Most programs were evaluated against standard care (Table 2).

Among all programs assessed, the 41 (64.1%) that measured clinical outcomes reported at least one positive response related to the program studied. Of the 41 measuring one or more adherence outcome, 27 (65.9%) reported at least one significantly positive adherence end point. Of 42 studies measuring one or more humanistic outcomes, 27 (64.3%) reported at least one significantly positive result. Relatively few programs reported an economic outcome (n=15). Of these, 12 reported at least one significantly positive economic end point (Figure 2).

Overall assessment of quality and risk of bias

Of the 64 studies, 46 (71.9%) used the highest quality randomized or cluster RCT design, followed by 16 (25%) that used lower quality retrospective and observational designs. Most studies adequately addressed reporting bias – 48 (75%), attrition bias – 37 (57.8%), and selection bias – 35 (54.7%). The most frequently identified bias was performance bias – 20 (31.2%) – which was primarily related to the lack of blinding of participants, personnel, and outcome assessors. This is likely an underestimate of performance bias, however, as 31 (48.4%) of the studies assessed contained inadequate information related to study procedures.

Table 2 Included programs, components and outcomes

Source	Disease state	Practitioner implementing	Service delivery mechanism	Study design/ comparator	Outcomes				Funding source(s)
					Adherence	Clinical	Humanistic outcomes (results direction)	Cost/utilization outcomes (results direction)	
Abdelhamid et al[19]	Asthma/ COPD	Pharmacist	C	RCT/standard care		Acute attacks, nocturnal asthma symptoms, peak expiratory flow rate, hospitalizations (mixed)	Self-reported sickness days (Pos)	Hospitalizations (Pos)	Private
Achieng et al[20]	HIV	Pharmacist, community health workers, physician	C, H	Prospective cohort/ nonprogram participants	90-day filled prescriptions (mixed)	Virologic failure (mixed)			Pharma/PBM
Aguado et al[21]	Cardiovascular disease/heart failure	Nurse	H	RCT/standard care		Mortality, hospitalizations, ED visits (mixed)	Functional status/ QOL (Neg)	Hospital/ED costs, ED (Pos)	
Al Hayek et al[22]	T2DM	Diabetes educators, physician	C	Prospective cohort/ baseline as control	Morisky Medication Adherence Scale (Pos)	Glycemic control (Pos)	Anxiety/ depression, self-care (mixed)		
Ali et al[23]	T2DM	Pharmacist	C	RCT/standard care plus one pharmacist session		Glycemic control, lipids, BMI, BP control (mixed)	Mixed satisfaction, functional status/ QOL (mixed)		Pharma/PBM
Amado Guirado et al[24]	Hypertension	Nurse	C	RCT/standard care	Haynes–Sackett and Morisky–Green self-reports and pill counts (mixed)	BP control, BMI (Neg)	Knowledge (Neg)		Govt
Antonicelli et al[25]	Cardiovascular disease/heart failure	MD led team	C, P	RCT/standard care	Compliance (unspecified) Pos	Mortality and hospitalization composite, BP control, ejection fraction, heart rate, lipids, electrolytes, urine output (mixed)	QOL (Neg) (Neg)	Hospital costs (unclear)	Govt
Böhme et al[26]	Cardiovascular disease/heart failure	Trained counselors	P	Prospective cohort/ baseline as control		Symptoms, impairment (Pos)	Perceived health (Pos)		Pharma/ PBM, private

(*Continued*)

Table 2 (*Continued*)

Source	Disease state	Practitioner implementing	Service delivery mechanism	Study design/ comparator	Outcomes				Funding source(s)
					Adherence	Clinical	Humanistic outcomes (results direction)	Cost/utilization outcomes (results direction)	
Cate et al[27]	Glaucoma	Interprofessional	C, P	RCT/standard care	Medication possession ratio via MEMSCAP/ Morisky Medication Adherence Scale (Neg)	Intraocular pressure (Neg)	Satisfaction (mixed)	Hospital costs (Neg)	Pharma/ PBM, Govt
Chiou et al[28]	HIV	Interprofessional	C, H, P	RCT/standard care	Customized adherence self-report questionnaire (Pos)	Viral load, $CD4^+$ (Pos)	QOL (Pos)		Pharma/PBM
Chung et al[29]	HIV	Trained counselors/ pharmacist	C, M	RCT/standard care plus one pharmacist session	Monthly pill counts (mixed)	Virologic failure, $CD4^+$, mortality (mixed)			Govt
Cleland et al[30]	Cardiovascular disease/heart failure	Nurse	H, P	RCT/standard care		Days lost to mortality, hospitalization (mixed)		Hospitalization, hospital days (mixed)	Pharma/PBM
Clifford et al[31]	T2DM	Pharmacist	C, P	RCT/standard care		Glycemic control, lipids, BP control, CHD/stroke risk (mixed)	QOL data not reported (Neg)		Private
Criswell et al[32]	Hypertension	Pharmacist	C, P	Cluster RCT/ standard care plus one study nurse visit	Modified Morisky scale (Neg)	Blood pressure, symptoms (Pos)	Self-efficacy, Social support (mixed)		Govt
Crowley et al[33]	Coronary risk reduction/ dyslipidemia	Nurse	E, P	RCT/standard care	Morisky Medication Adherence Scale (Pos)	Glycemic control, lipids, BP control (Neg)			Govt
de Bruin et al[34]	HIV	Nurse	C	RCT/standard care	MEMSCAP (mixed)	Viral load suppression (Pos)	Usefulness (Pos)		Private
Del Sindaco et al[35]	Cardiovascular disease/heart failure	MD and nurse	C, H, P	RCT/standard care		Death, exacerbation leading to hospitalizations (mixed)	QOL, health status (unclear)	Hospital costs (Pos)	Private
Dilorio et al[36]	HIV	Nurse	C, P	RCT/standard care	MEMSCAP (mixed)	Viral load, $CD4^+$, (Neg)			Govt
Erhun et al[37]	Hypertension	Pharmacist	C	Prospective cohort/ retrospective data as control	Missed dose incident (unclear)	BP control (Pos)	Satisfaction (Pos)		

Evans et al[38]	Coronary risk reduction/ dyslipidemia	Pharmacist	C, E, H, M, P	RCT/standard care	Proportion of days covered (Neg)	Framingham risk score, lipids, blood pressure (Neg)			Govt
Gabbay et al[39]	T2DM	Nurse	C, E, P	RCT/standard care		Glycemic control, lipids, BP control (mixed)	Satisfaction, self-care, QOL (mixed)		Private
Grosset and Grosset[40]	Parkinson's disease	Physician	C	RCT/standard care	MEMSCAP (Pos)	Disease progression, adverse events (Neg)	QOL (Neg)		Private
Heisler et al[41]	T2DM	Pharmacist	C, M, P	Cluster RCT/ printed education materials only		Glycemic control, lipids, BP control (Neg)			Govt
Hlubocky et al[42]	Renal transplant/ failure	Pharmacist	M, P	Retrospective cohort study/ retrospective data as control	Continuous measures of medication adherence (unclear)	Need for hospitalization (Neg)	Satisfaction (Pos)	Program revenue after expenses, readmissions, length of stay (mixed)	Private
Hohmann et al[43]	Cerebral vascular disease	Pharmacist	C	Non-randomized RCT/standard care		Physical functioning (mixed)	Satisfaction (Pos)		Private
Holzemer et al[44]	HIV	Nurse	C, P	RCT/standard care	MEMS, pill count, self-report AIDS clinical trial group, Morisky Medication Adherence Scale (Neg)	Viral load, $CD4^+$ (unclear)			Govt
Jacobs et al[45]	T2DM/ hypertension/ high cholesterol	Pharmacist and MD	C, P	RCT (pragmatic)/ standard care		Glycemic control, lipids, blood pressure (Pos)			Pharma/PBM
Jorstad et al[46]	Cardiovascular disease/heart failure	Nurse	C	RCT/outpatient clinic visits, referral to rehab per country guidelines	Self-reported maximum adherence (Neg)	Coronary risk, need for hospitalization (mixed)	Smoking, lifestyle changes (mixed)	Hospital readmissions (Pos)	Pharma/PBM
Kennedy et al[47]	Rheumatoid arthritis	Interprofessional	C	Quasi-experimental, controlled/ waitlisted control crossover		Self-efficacy, health assessment questionnaire (Neg)	Knowledge, illness intrusiveness, coping (Neg)		Pharma/PBM
Koenig et al[48]	HIV	Nurse	C	RCT/standard care	MEMSCAP (Pos)	Viral suppression, $CD4^+$ (Neg)			Govt
Lai et al[49]	Osteoporosis	Pharmacist	C, P	RCT/standard care, plus information package at 12 months	Self-reported adherence (mixed)	Bone turnover markers (Neg)	Knowledge, QOL, satisfaction (Pos)		Govt

(*Continued*)

Table 2 (*Continued*)

Source	Disease state	Practitioner implementing	Service delivery mechanism	Study design/ comparator	Outcomes				Funding source(s)
					Adherence	Clinical	Humanistic outcomes (results direction)	Cost/utilization outcomes (results direction)	
Liekweg et al[50]	Breast, ovarian cancer	Pharmacist	C	Prospective cohort/ standard care in control cohort		Chemotherapy related nausea, emesis (mixed)	QOL, satisfaction, (Pos)		Private
Maduka and Tobin-West[51]	HIV	Trained counselors	C	RCT/standard care	Self-reported pills missed (Pos)	$CD4^+$ (Pos)	Knowledge (Pos)		Private
Márquez Contreras et al[52]	Hypertension	Physician	M, P	RCT/standard care	Pill counts (Pos)	BP control (Pos)			Pharma/PBM
McDermott et al[53]	Coronary risk reduction/ dyslipidemia	Trained counselors	P	RCT/standard care	Brief medication questionnaire (Neg)	Lipids (mixed)	Knowledge, patient activation, self-efficacy in physician communication (mixed)		
Morgado et al[54]	Hypertension	Pharmacist	C	RCT/standard care	Morisky Medication Adherence Scale (Pos)	BP control (Pos)	Knowledge (Pos)		Govt
Mugusi et al[55]	HIV	Nurse	C	RCT/standard care with monthly adherence counseling	Self-reported adherence (Neg)	$CD4^+$ (Neg)			Govt
Nieuwkerk et al[56]	Coronary risk reduction/ dyslipidemia	Nurse	C	RCT/standard care	Self-reported adherence (Pos)	Lipids, anxiety (mixed)	QOL, risk perception (Neg)		Pharma/PBM
Ogedegbe et al[57]	Hypertension	Research assistants	C	RCT/standard care	MEMSCAP (Pos)	BP control Neg			Govt
Phumipamorn et al[58]	T2DM	Pharmacist	C	RCT/standard care	Pill counts (Pos)	Glycemic control, lipids (mixed)	Knowledge (Pos)		Govt
Ruan et al[59]	HIV	Not clear	P	Prospective cohort/ baseline as control		Viral suppression (Pos)			Govt
Sadik et al[60]	Cardiovascular disease/heart failure	Pharmacist	C, I	RCT/standard care	Self-reported adherence (Pos)	2-minute walk test, BP control, weight, forced vital capacity (Pos)	QOL, knowledge (mixed)		
Sauvageot et al[61]	T2DM/ hypertension/ high cholesterol	Pharmacist and patient advocate	Ph	Retrospective cohort/baseline as control		Glycemic control, lipids, blood pressure (mixed)			Private

Shanmugam et al[62]	Asthma/ COPD	Pharmacist	C	RCT/standard care		Asthma control, Peak expiratory flow rate (Pos)	QOL (Pos)		Private
Sisk et al[63]	Cardiovascular disease/heart failure	Nurse	C, M, P	RCT/standard care		Need for hospitalization, physical functioning (mixed)	Knowledge, QOL (mixed)	Hospitalizations (Pos)	Govt
Skowron et al[64]	Hypertension	Pharmacist	C	Quasi-RCT/ randomize pharmacists to provide intervention or standard care		BP control (Neg)	Knowledge, QOL (Neg)		
Solomon et al[65]	Osteoporosis	Health educator	P	RCT/standard care plus mailed information	Medication possession ratio, persistence (Neg)	Fractures, falls, depression (Neg)	Satisfaction (unclear)		Govt
Sriram et al[66]	T2DM	Pharmacist	C, P	RCT/standard care		Glycemic control, BMI (Pos)	QOL, satisfaction (Pos)		Private
Stockl et al[16]	Multiple sclerosis	Pharmacist	P, M	Retrospective cohort study/ standard care in non-participating cohort	Medication possession ratio, persistence (Pos)	Relapses (Pos)	QOL, employment (Neg)		Pharma/PBM
Stockl et al[17]	Rheumatoid arthritis	Pharmacist	P, M	Retrospective cohort study/non-participating cohort	Proportion of days covered, persistence, switching (mixed)	Physical functioning, Health assessment questionnaire (mixed)	QOL, employment productivity (mixed)	Pharmacy costs (mixed)	Pharma/PBM
Stone et al[67]	T2DM	Nurse	H, P	RCT/monthly care coordinator phone call		Glycemic control, lipids, blood pressure (mixed)			Govt
Stroup et al[68]	Osteoporosis	Pharmacist	C, P	Prospective cohort/ baseline as control		Bone mineral density, *T*-score (mixed)			Private
Tan et al[69]	Multiple sclerosis	Nurse	P, M	Retrospective cohort study/ nonparticipant controls	Medication possession ratio, persistence (Pos)	Hospitalizations, mixed		Hospital/pharmacy costs (mixed)	Pharma/PBM
Thompson et al[70]	Cardiovascular disease/heart failure	Nurse	C, H	RCT/standard care	Hill–Bone compliance to high blood pressure therapy scale (Neg)	Event-free survival, mortality, need for hospitalization (mixed)	QOL (Neg)	Hospital readmissions, length of stay (Pos)	Pharma/PBM
Triller and Hamilton[71]	Cardiovascular disease/heart failure	Nurse and pharmacist	C, H, P	RCT/standard care		Hospitalization, mortality (Neg)	QOL (Neg)	Hospital, health system, and home care costs (Neg)	Govt

(*Continued*)

Table 2 (*Continued*)

Source	Disease state	Practitioner implementing	Service delivery mechanism	Study design/ comparator	Outcomes				Funding source(s)
					Adherence	Clinical	Humanistic outcomes (results direction)	Cost/utilization outcomes (results direction)	
Tschida et al[72]	Renal transplant/ failure	Pharmacist	P	Retrospective cohort study/ nonparticipant controls	Medication possession ratio, medication gaps, persistence (Pos)	Mortality, transplant related complications, need for hospitalization (Neg)		Total health care costs, hospitalization, office visits, transplant costs (mixed)	Pharma/PBM
Van Camp et al[73]	Renal transplant/ failure	Nurse	C, P	Prospective cohort/ baseline as control	MEMSCAP, self-reported adherence (Pos)	Phosphate, calcium, parathyroid hormone (mixed)	Knowledge (Pos)		
Villeneuve et al[74]	Coronary risk reduction/ dyslipidemia	Pharmacist and physician	C	Cluster RCT/ standard care	Pills dispensed (Neg)	BP control, BMI, glycemic control, coronary risk factors (Neg)	Lifestyle changes (Pos)		Pharma/PBM
Wang et al[75]	Hypertension	Pharmacist	C, P	RCT/standard care	Modified Morisky scale (Pos)	BP control (Pos)			
Wang et al[76]	Asthma/ COPD	Nurse, Pharmacist	C	RCT/standard care	Self-assessment of medication adherence questionnaire (Neg)	Asthma symptoms (unclear)	QOL, knowledge (mixed)		
Wei et al[77]	Asthma/ COPD	Pharmacist	C, P	RCT/standard care	Self-reported missed doses, pill counts (Pos)	Hospitalization due to acute exacerbation (Pos)	QOL (Neg)	Hospitalizations (Pos)	
Winter et al[78]	HIV	Not clear	C	Retrospective cohort study/ non program participants	Appointment adherence/ abandonment (mixed)	$CD4^+$ (Neg)			Private
Wu et al[79]	T2DM	Nurse	C, P	Quasi-experimental (randomized pre-posttest)/standard care		Social support, functioning, depression (Neg)	QOL, social support (Neg)		
Zolfaghari et al[80]	T2DM	Nurse	P	Quasi-experimental (pre-posttest)/ phone message vs phone call	Self-reported adherence (Neg)	Glycemic control (Neg)	Lifestyle changes (Neg)		

Abbreviations: BP, blood pressure; BMI, body mass index; C, clinic; COPD, chronic obstructive pulmonary disease; CHD, coronary heart disease; E, Email; ED, emergency department cost/utilization of services; Govt, government funded; HIV, human immunodeficiency virus; H, hospital costs/utilization of hospital services; I, inpatient; M, mail; MD, medical doctor; MEMS, medication event monitoring system; MEMSCAP, MEMS cap; Neg, negative outcome; P, phone; PBM, pharmacy benefit manager funded; Ph, pharmacy; Pharma, pharmaceutical industry funded; Pos, positive outcome; QOL, quality of life; RCT, randomized controlled trial; T2DM, type 2 diabetes mellitus.

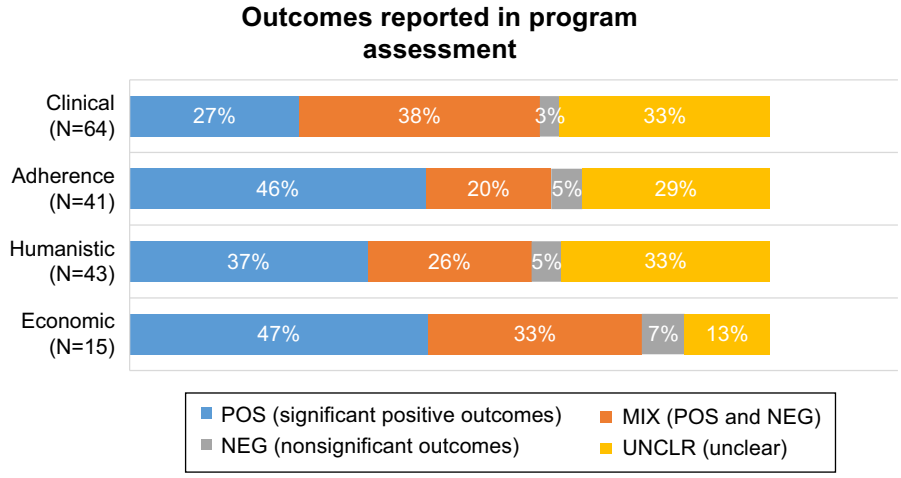

Figure 2 Overall outcome results in patient support programs assessed.

Discussion

In the decades following the passage of the Medicare Modernization Act and the rise of managed care, health professionals, payers, and policymakers have sought to lower costs and improve care quality associated with chronic illness. Medication-focused PSPs have taken a variety of forms, evolving with disease management and medication therapy management, among others. This targeted review is the first to attempt to describe the structure, methods, and outcomes reported in the literature for PSPs. Of the 64 studies, the majority of the interventions were conducted by a health care professional (HCP) in various clinical settings. This included outpatient clinics, primary care practices, inpatient hospital settings, and services conducted at the patient's home by nurses, pharmacists, physicians, and other health care team members. Interventions included verbal counseling sessions, scheduled follow-up telephone calls, and discharge training sessions. Other indirect patient services included text messaging, refill reminder calls, and written educational materials provided regularly to the patient.

Adherence measures were found to be the most positively impacted through the use of PSPs, followed by humanistic outcomes (eg, patient reported outcomes, quality of life, functional status). PSPs that operated in a clinic (with or without additional phone services) were identified as the most common service in this targeted review. Although clinical outcomes were evaluated most frequently compared to the other measures, there was less evidence supporting the positive impact of this outcome. Minimal evidence was reported for studies focusing on cost, particularly PSPs' impact on total medical costs, where the majority of health care dollars are spent. Where hospital utilization was assessed, a trend toward reduction in utilization was observed, suggesting that PSPs may provide a benefit in intervening prior to hospitalization becoming necessary.

The evaluation for adherence varied across disciplines and the type of interventions, including face-to-face encounters, group teaching, regular refill reminders, and mailed communications. The method of delivery of these services was heterogeneous, and evidence suggests that PSPs can lead to a positive impact toward patient medication adherence. It can also be suggested that increased patient education combined with regular interventions contribute toward improved patient adherence. Positive benefits were realized for both adherence and humanistic outcomes resulting from face-to-face interventions during a patient encounter, in addition to educational materials supplementing the patient's understanding. Similarly, existing literature, including that of Warsi et al,[10] found that interventions in providing patient and provider reminders, patient education, and financial incentives improved the quality of care for patients with chronic disease. They also showed that two or more interventions were more likely to be successful than a single intervention. Many studies in our targeted review reported two or more interventions for positive adherence and humanistic outcomes, demonstrating a possible increased benefit compared to a single intervention.

Our review was not without limitations. Due to the high volume of initial hits, we limited our search strategy to two databases, PubMed/Medline and Web of Science. A broader search in additional databases may have yielded additional citations. When examining the results of all outcomes in light of study quality, single-armed cohort studies, in which patients served as their own controls at baseline, produced more positive results across the outcomes measured. It is not clear if this methodology overoptimistically portrays

results, as RCTs with standard care as a comparator led to more mixed and negative results. Accordingly, there is a need for further evidence surrounding the clinical and financial benefits of PSPs.

Implications to clinical practice and industry

Our analysis found that support programs are heterogeneous with regard to medical conditions served, therapeutic drug classes included, methods of delivery, and funding source. The range of study designs included in this analysis (eg, randomized-controlled trials, cohort, nonrandomized) allows for some generalization to real-world situations and application in a variety of settings. The findings are relevant to PSP developers and HCPs interested in improving the care of chronic, debilitating, and costly disease. They also reveal meaningful gaps in the empiric evidence supporting the use of PSPs.

Unexpected was such a large proportion of PSPs being sponsored by entities, including PBMs and the pharmaceutical industry. While never intended to directly provide health care or replace the role of HCPs, the growth of non-HCP-sponsored programs suggests a genuine need to support the medical professional's advice beyond time-constrained office visits. Our findings suggest that non-HCP entities may play an increasingly important role in developing and implementing these programs. PSPs supported by these stakeholders target a wide audience through large health plans. For example, Stockl et al[16] invited patients with multiple sclerosis (MS) to participate in an enhanced disease therapy management program offered through a PBM, to improve adherence and maximize quality of life. Participants received clinician telephone consultations, care plan mailings, and educational material mailings based on a predefined schedule for up to 6 months post enrollment. An initial phone consultation typically lasted 40–60 minutes, and follow-up consultations lasted 20–30 minutes. During each consultation, the clinician assessed patient knowledge and health concerns and provided education on core topics. Each clinician developed a personalized care plan that summarized the telephone consultation and sent it to the patient and the prescriber of the injectable medications. Patients also received monthly educational mailings specific to MS for 6 months. Patients participating in the program had significantly higher injectable MS medication adherence compared with community pharmacy patients. In addition to increased adherence and persistence with injectable MS medications, a clinical benefit of lower MS relapse was also observed.

In a similar program, also nested in a PBM,[17] patients with an injectable RA medication were enrolled into a therapy management program. The primary goal was to facilitate improved adherence to injectable RA medications, and with participation, patients reported significant improvements in physical functioning and work productivity. These two examples illustrate the potential benefits of multifaceted PSPs on medication use as well as clinical and humanistic outcomes.

Given the rising cost of complex diseases such as arthritis, MS, and oncology, the implementation of PSPs should be considered to maximize health outcomes and value in patient-focused care. The site or origin of service is a factor to consider when evaluating program effectiveness. Existing literatures have explored the impact of pharmaceutical services provided in the ambulatory and community settings. Singhal et al's[18] systematic review focused on pharmacist-provided support and revealed evidence that "pharmaceutical services in community and ambulatory care settings make a positive impact on patient outcomes". Interventions included patient counseling performed by the pharmacist, weekly refill reminders, and scheduled patient follow-up visits that positively impacted clinical, humanistic, and economic outcomes.

Patients and HCPs have not universally embraced services offered through PSPs. Reasons for this are beyond the scope of this targeted review. It is, however, noteworthy that a preponderance of the published evidence corroborates the utility of PSPs for common chronic illnesses to the extent that PSP sponsors can demonstrate improved outcomes from their programs, and HCPs and their patients stand to benefit from participation.

Applicability of findings

The rapid growth in the development and availability of specialty pharmaceuticals combined with fundamental changes in health care delivery are helping to drive new models of care where efficiencies and outcomes are taken into serious account. Conditions that often required hospitalization, treatment administration by a HCP, or very close monitoring can now be treated with medications through retail and specialty pharmacies. By transferring responsibility for obtaining and administering complex and costly medications to patients in the community setting, patient behavior becomes a major influence on the effectiveness and costs of care. Therefore, at least in theory, efforts aimed at improving otherwise unfavorable behaviors regarding medication use should enhance effectiveness, mitigate waste

and inefficiency, and improve both treatment satisfaction and outcomes. PSPs intend to achieve such results within discrete populations of greatest perceived need. While still limited in evidentiary strength, the published evidence suggests that the majority of sophisticated, "high-touch" PSPs are having the intended effect.

Limitations of evidence

A systematic review, by its nature, is subject to synthesize information from existing literature and can consequently lead to probable publication bias. Due to the inclusion criteria of this study, articles evaluated were published in English, likely to be cited more frequently, and be presented as a positive study. The majority of the trials included in this review were less methodologically robust as even RCTs relied on heterogeneous control arms in the form of "usual care". Literature evaluated included quasi-experimental, prospective observational cohort studies, retrospective cohort studies, and RCTs.

Although this review identified evidence for clinical and economic outcomes for PSPs, the constraints for populations, interventions, and settings identified in this systematic review may limit its applicability. Many studies evaluated in this review provided insufficient detail to understand the quality of the interventions. For instance, patient self-reporting was implemented in a number of studies, but this approach can limit the accuracy and validity of the results presented. While the preponderance of data are positive or neutral in outcome, a minority of studies report negative findings, particularly in the economic category of outcomes. It remains unknown if this truly reflects the success of PSPs or underpublication of negative findings.

Suggestions for future research

This review is meant to describe the current state of PSPs from a broad public health perspective. Further comparative analysis within the most common medical conditions may illuminate the specific interventions, methods of delivery, and origin of program components that are most beneficial for a given disease state. Additionally, methodologic rigor in study design is heterogeneous, which highlights a need for greater use of valid comparison groups, standardization of outcomes measured, and greater use of end points that quantify the economic benefits of PSPs. The underrepresentation of clinical, humanistic, and economic outcomes compared to medication adherence illustrates important gaps in this body of evidence. Additionally, there is a need for reporting of both negative and positive findings associated with specific programs so that developers may build upon the experience of others when constructing support programs.

Conclusion

Our review was the first to broadly evaluate the impact of PSPs on adherence, clinical, humanistic, and economic outcomes. The growing implementation of these programs in the pharmaceutical industry, specialty pharmacies, and life-science companies coexist with the need to further explore the utilization of these programs. Little is known about the costs associated with PSPs, and further research is needed to determine the effectiveness of different implementation strategies on adherence, clinical, humanistic, and economic outcomes in PSPs.

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