



The Impact of Patient Support Programs in Europe: A Systematic Literature Review

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Abstract

Background and Objective Patient support programs aim to provide solutions beyond the medication itself, by enhancing treatment adherence, improving clinical outcomes, elevating patient experience, and/or increasing quality of life. As patient support programs increasingly play an important role in assisting patients, numerous observational studies and pragmatic trials designed to evaluate their impact on healthcare have been conducted in recent years. This review aims to characterize these studies.

Methods A systematic literature review, supplemented by a broad search of gray literature, was conducted following PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) and Cochrane recommendations. Observational studies and pragmatic trials conducted in Europe to evaluate the impact of patient support programs, published in English or Spanish between 17/03/2010 and 17/03/2020, were reviewed. Two patient support program definitions were applied starting with Ganguli et al.'s broad approach, followed by the European Medicines Agency definition, narrowed to Marketing Authorization Holders organized systems and their medicines. The quality of publications was assessed using the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement 22-item checklist.

Results Of the 49 identified studies following the Ganguli et al. definition, 20 studies met the European Medicines Agency definition and were reviewed. Patient support program impact was evaluated based on a wide range of methodologies: 70% assessed patient support program-related patient-reported outcomes, 55% reported clinical outcomes, and 25% reported economic impacts on health resources. Only 45% conducted a comparative analysis. Overall, 75% of the studies achieved their proposed objectives.

Conclusions The heterogeneity of the observational studies reviewed reflects the complexity of patient support programs that are built ad hoc for specific diseases, treatments, and patients. Results suggest that patient support programs play a key role in promoting treatment effectiveness, clinical outcomes, and satisfaction. However, there is a need for standardizing the definition of patient support programs and the methods to evaluate their impact.

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Key Points

We appraised 49 studies aimed at evaluating patient support programs conducted in Europe in the last 10 years. Among them, 40% were sponsored by a marketing authorization holder and related to medicinal products.

In general, studies showed a positive impact of patient support programs on patients' adherence to medication, satisfaction, or health-related quality of life. In addition, patient support programs ameliorate clinical outcomes or reduce the use of resources and costs.

However, the heterogeneity of the observational studies in terms of design and outcomes makes it difficult to determine to what extent patient support programs provide additional value to the standard of care. Therefore, there is a need to standardize the definition of patient support programs and the methods to evaluate their impact on health outcomes.

1 Introduction

Patient support programs (PSPs) aim to provide solutions beyond the medication itself, adding complementary value to medicinal products by supporting patient care. Historically, PSPs have been defined as enhanced self-management support programs that include interventions such as individualized medication counseling, training, support, and virtual reminders to improve medication-taking behavior [1]. This definition encompasses a variety of patient-directed interventions, from educational programs aimed at improving disease management, regardless of the patient's treatment, to specific programs that aim to provide education to patients and a follow-up on patients receiving a particular medicine. The European Medicines Agency (EMA) has adopted a more narrow definition for PSPs, recognizing only organized systems in which a Marketing Authorization Holder (MAH) receives and collects information relating to the use of its medicinal products [2].

Independently of the PSP definition, the majority of these programs fall into one or more of the following three categories: (1) supporting patients and helping them take their medications as prescribed; (2) helping patients to understand their condition and providing advice on managing the disease (e.g., lifestyle, exercise, and diet); and (3) providing a service or financial assistance or reimbursement support to patients (also known as patient assistance programs) [3]. The common goal of these programs is to enhance treatment

adherence, improve clinical outcomes, elevate the patient experience with treatment, and/or increase their quality of life.

As PSPs increasingly play an important role in assisting patients with chronic conditions, the number of programs has increased significantly in recent years [1]. Marketing Authorization Holders have launched worldwide PSPs for newly authorized products and numerous observational studies designed to evaluate their impact on healthcare are being reported. A meta-analysis showed that PSPs improve treatment adherence and persistence in the therapeutic area of inflammatory and immunologic diseases [4]. A systematic literature review also described the positive impact of PSPs on adherence, clinical, and humanistic outcomes in chronic diseases [1]. Nonetheless, that review also found that study designs and outcomes reported in the literature were highly heterogeneous owing to different factors such as the purpose of the PSP, type of services and actions provided, disease and medication therapy management, or stakeholders' involvement [1]. In addition, no guidelines and recommendations from experts and/or authorities exist to guide the development of PSPs, further promoting the heterogeneity between PSPs and, consequently, of the studies that evaluate them. This review aims to characterize the observational studies and pragmatic trials conducted to evaluate PSPs in Europe, with emphasis placed on study results and outcomes.

2 Methods

2.1 Data Source and Strategic Approach

A targeted systematic literature review of international databases (MEDLINE/PubMed, Medicina en español [MEDES], and Índice Bibliográfico Español en Ciencias de la Salud [IBECS]), supplemented by a broad search of gray literature, was performed to identify observational studies and pragmatic trials that have evaluated the impact of PSPs in Europe over the last 10 years. The search was conducted under the "Preferred Reporting Items for Systematic Reviews and Meta-analysis: The PRISMA Statement" and Cochrane guidelines by using search filters and standardized terms [5, 6] (Table S1 of the Electronic Supplementary Material [ESM]).

2.2 Publication Selection and Data Extraction Procedures

Two independent reviewers (LPC and MC) screened publications retrieved based on the title and/or abstract. Full texts of retrieved publications were peer reviewed and ascertained for final eligibility if they meet inclusion/exclusion criteria

according to the PICOTS framework [7] (Table 1). Discrepancies were resolved by consensus or by involving a third team member (LL).

A first screening applying a broad approach was used to identify PSP-related articles based on the definition of PSP provided by Ganguli et al. [1]: “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 aim is to help patients better manage their disease and complex medications regimes, improve medication adherence, and reduce complications and related costs”. A second screening according to the EMA definition for PSP [2]: “an organized system where a marketing authorization holder receives and collects information relating to the use of its medicinal products” was applied to (1) adopt the definition of PSPs in Europe, according to the EMA Good Vigilance Practice Module VI, in order to remain within a common overarching regulatory framework for the conduct and evaluation of PSPs, (2) reduce the heterogeneity among the intervention evaluated, (3) provide additional and complementary information to that provided by Ganguli et al., and (4) explore the role of MAHs beyond the medication itself. Hence, the second screening analyzed PSPs involving a specific medication, disease, and MAHs. All data were extracted by two independent reviewers (LPC and MC). A standardized data extraction form and data extraction guidelines were used. The characteristics of the reviewed studies were further described based on the study’s outcomes (patient-reported outcomes [adherence, satisfaction, and quality of life], clinical, or economic). In addition, each study’s outcome was assessed based on the achievement of

pre-defined objectives and classified as ‘objective achieved,’ ‘objective not achieved,’ ‘inconclusive,’ or ‘not defined a priori’. The quality of publications was assessed using the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement 22-item checklist [8]. The quality assessment is provided in Table S2 of the ESM.

3 Results

As shown in the PRISMA flow diagram (Fig. 1), a total of 5228 studies were identified in the databases that were consulted. After duplicate removal, the title and abstract of the resulting 5216 publication records were screened for information relevant to the analysis, resulting in the exclusion of 5110 records. Of the 106 remaining publications, 57 were discarded after full-text reading because of non-compliance with eligibility criteria. In the first broader approach, where any type of intervention on patients was allowed (Ganguli et al. definition [1]), 49 publications were selected. These publications included observational studies that evaluated a wide variety of PSPs. However, 29 of them did not meet the EMA definition and were not selected after the second screening round [2] because they were not linked to a specific drug or medical device (55%; $n = 16$), and were not funded or initiated by a pharmaceutical company (45%; $n = 13$) [Fig. 1 and Table S3 of the ESM]. Hence, 20 studies focused on PSPs sponsored by a pharmaceutical company and related to a specific medical drug were finally included in the review.

Table 1 PICOTS criteria

Study characteristics	Eligible	Ineligible
Patient population	Not limited to a specific disease or group of diseases	NA
Intervention	PSPs that meet the EMA PSP definition: linked to a specific product and sponsored by a pharmaceutical company	PSPs promoted by a national health system of European countries PSPs not linked to a specific product PSPs not initiated by the pharmacological industry PSPs linked to non-pharmacological interventions (i.e., medical devices) PSPs initiated by industry but not linked to a specific product, but related to a disease
Comparison	NA	NA
Outcomes	Clinical Economic PROs (e.g., adherence/persistence, QoL, satisfaction)	NA
Study design	Observational studies and pragmatic trials	Experimental designs PSP evaluation in the pilot phase
Time frame	17/03/2010–17/03/2020	Publications before 17/03/2010 or after 17/03/2020
Language	English and Spanish publications	Non-English or non-Spanish publications
Country	European countries	Countries outside Europe

NA not applicable, EMA European medicines agency, PROs patient-reported outcomes, PSPs patient support programs, QoL quality of life

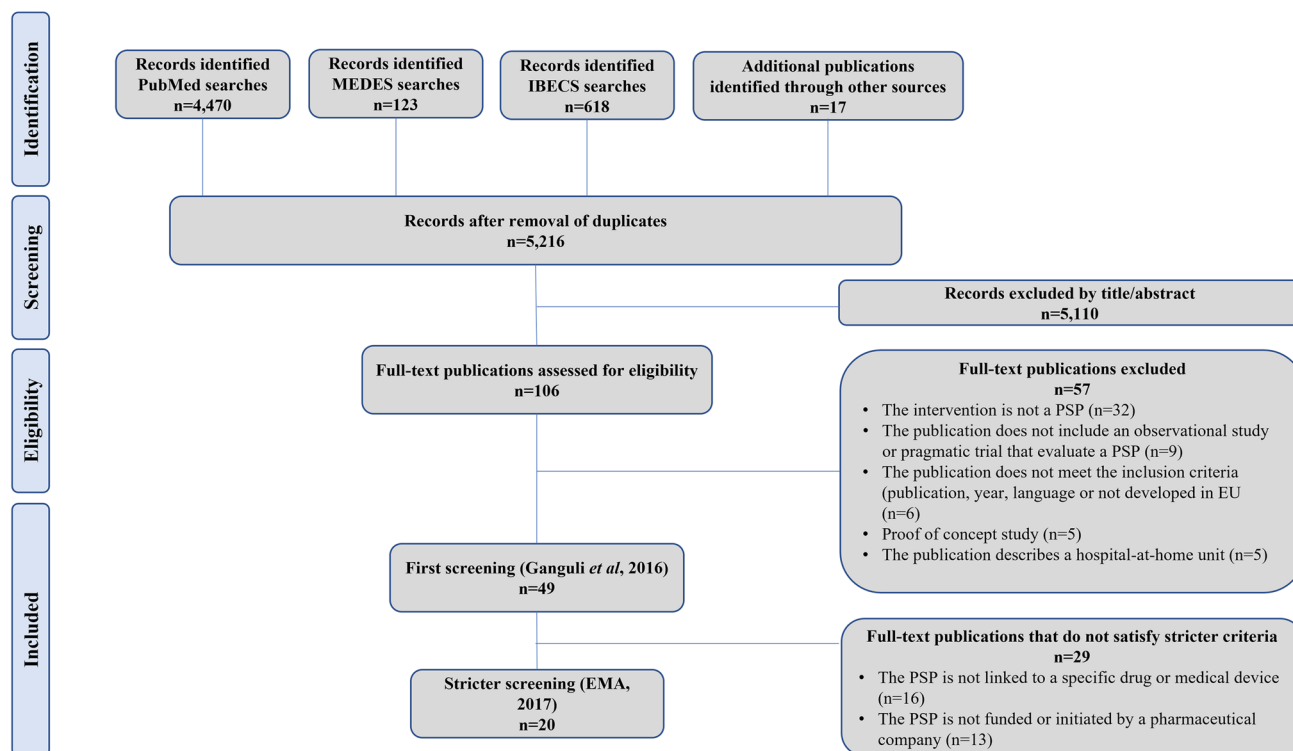


Fig. 1 Flow diagram of study selection following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guideline. *EMA* European Medicines Agency, *PSPs* patient support programs

3.1 Characteristics of the Reviewed Studies

Tables 2 and 3 summarize the main characteristics of the 20 studies regarding PSPs that met the EMA definition. All studies were classified as observational (no pragmatic trials identified), designed as prospective (50%, $n = 10$) [9–18], retrospective (25%, $n = 5$) [19–23], cross-sectional (20%, $n = 4$) [24–27] (three of which were surveys), or patient-case report studies (5%, $n = 1$) [28].

Only 45% of the studies ($n = 9$) conducted a comparative analysis to determine the benefits or effectiveness of PSPs; 35% ($n = 7$) compared a no-PSP control arm (standard care) to a PSP (intervention group) and another 10% ($n = 2$) performed before-and-after intervention comparisons.

Most of the PSPs evaluated in the studies reviewed targeted patients with diabetes mellitus [16–18, 22, 23, 27] multiple sclerosis [10, 11, 20, 21, 24], rheumatoid arthritis [12, 13], osteoporosis [14, 19], psoriasis [25, 26], non-Hodgkin lymphoma [28], colorectal and breast cancer [9], and various types of diseases [15] that met MAH's indications for a specific treatment (Tables 2 and 3).

The studies included in the review evaluated eight specific PSPs, most of which (87.5%; $n = 7$) provided educational programs on treatment and related diseases along with monitoring of patients, via telephone calls ($n = 5$; 62.5%), face-to-face visits ($n = 3$; 37.5%), or e-mail contacts ($n = 2$;

10%). In addition, two PSPs (25%) provided home delivery of medications and/or medical devices (i.e., needles). Nurses were the healthcare professionals most frequently involved in PSPs (see details in Table S4 of the ESM).

3.2 Results from the Reviewed Studies

To evaluate the impact of the PSPs, different outcomes were assessed. Most of the studies (70%; $n = 14$ [9–12, 14, 15, 19–22, 24, 25, 27, 28]) used patient-reported outcome measures: nine of them to record adherence and persistence ($n = 2$ evaluated patients' reported PSP persistence and $n = 7$ evaluated patients' reported treatment adherence), eight to assess patient satisfaction, and three to collect patients' health-related quality of life [HRQoL] ($n = 3$); 55% ($n = 11$ [10, 12, 15–18, 22, 23, 25–27]) reported on clinical outcomes achieved by patients participating in the PSP including safety outcomes ($n = 1$), and 25% ($n = 5$; [10, 12, 13, 15, 25]) assessed the economic impact of PSPs to determine the impact on health resource use and associated costs (Table 2).

Different instruments were used to evaluate the impact of the PSPs. Satisfaction with PSPs was assessed using either a 10-point Likert scale [22, 24, 27] or an ad hoc questionnaire developed for the study [14, 28]. In two studies, treatment satisfaction was evaluated using the Treatment Satisfaction

Table 2 Summary of the type of studied PSPs

Methodological characteristics	Results		
	N	%	References
Type of study according to collection timing			
Retrospective	5	25%	[19–23]
Prospective	10	50%	[9–18]
Cross-sectional	4	20%	[24–27]
Patient case report	1	5%	[28]
Total	20	100%	
Comparison			
No	11	55%	[12, 14, 15, 17–22, 24, 28]
Yes	9	45%	
Before/after	(2)		[10, 11]
Two arms (standard of care vs PSP)	(7)		[9, 12, 13, 16, 23, 25, 26]
Total	20	100%	
Therapeutic areas			
Type 2 diabetes mellitus	6	30%	[16–18, 22, 23, 27]
Multiple sclerosis	5	25%	[10, 11, 20, 21, 24]
Rheumatoid arthritis	2	10%	[12, 13]
Osteoporosis	2	10%	[14, 19]
Psoriasis	2	10%	[25, 26]
Non-Hodgkin lymphoma	1	5%	[28]
Colorectal and breast cancer	1	5%	[9]
ADA-treated patients with various pathologies	1	5%	[15]
Total	20	100%	
Evaluated outcome^a			
PROs	14	70%	[9–12, 14, 15, 19–22, 24, 25, 27, 28]
Adherence/persistence ^b	(9)		
Satisfaction ^c	(8)		
QoL	(3)		
Clinical	11	55%	[10, 12, 15–18, 22, 23, 25–27]
Economic	5	25%	[10, 12, 13, 15, 25]
Total	30	150%	
Setting			
Multinational	4	20%	[11, 12, 25, 26]
National	16	80%	[9, 10, 13–24, 27, 28]
Total	20	100%	

ADA adalimumab, PROs patient-reported outcomes, PSPs patient support programs, QoL quality of life

^aThere may be more than one type of variable evaluated per study

^b $n = 2$ evaluated patients' reported PSP persistence and $n = 7$ evaluated patients' reported treatment adherence

^c $n = 2$ evaluated treatment satisfaction and $n = 6$ evaluated satisfaction to PSP

Questionnaire for Medication [12, 15]. One study did not specify the methodology [25].

Improvements in patient adherence to medication were estimated as (1) percentage of doses taken/doses prescribed at different timepoints of the follow-up [9, 10], (2) percentage of patients who were recorded as having persisted with therapy during the study period [11, 19], and (3) percentage of patients who self-reported adherence (ad-hoc questionnaire or Morisky Medication Adherence Scale 4 questions)

[15, 20, 21]. Two studies assessed PSP persistence by reporting on the percentage of patients remaining in the program during the study follow-up [14, 27]. Several HRQoL questionnaires, both generic (EQ-5D, SF-12, SF-36) [15, 24] and disease specific (MusiQoL, SIBDQ, DLQI, ASQoL) [10, 15], were used to determine the impact of PSPs on patients' HRQoL.

Two approaches were used in the studies reviewed to assess the impact of the PSP on costs. First, five studies

Table 3 Main characteristics of selected publications

Author, year (country)	Type of observational study	Study population (size and disease)	PSP evaluated (funder)	Objective of the study	Outcomes evaluated in the study	Main results	Main objective achieved	STROBE
Afán de la Ribera et al., 2019 [23] (Spain)	Retrospective comparative study	67 patients with type 2 diabetes mellitus	T-Coach® PSP (Sanofi)	To assess the effectiveness of the T-Coach® program by comparing patients who completed the program with those who did not	<i>Clinical outcomes:</i> improve metabolic control and optimize treatment	Improvement by increase in patients with lower HbA1c (basal blood glucose)	Yes	NA ^a
Bellido Castañeda et al., 2019 [22] (Spain)	Retrospective study	589 patients with type 2 diabetes	T-Coach® PSP (Sanofi)	To analyze the effect of T-Coach® program on glycemic control of patients treated with insulin Glargine U300	<i>Clinical outcomes:</i> achieve blood glucose target <i>PROs:</i> satisfaction	Glycemic control reached by 75.7%, 77.6–73.6% of patients in the following 3, 6, and 12 months after inclusion 9 out of 10 patients satisfied	Yes	NA ^a
Bellido Guerrero et al., 2019 [18] (Spain)	Prospective study	589 patients with type 2 diabetes	T-Coach® PSP (Sanofi)	To evaluate whether this program was effective in helping patients reach their OID	<i>Clinical outcomes:</i> achieve target FBG and OID	77.6% of patients reached OID at 6 months	Yes	NA ^a
González et al., 2019 [27] (Spain)	Cross-sectional study	230 patients with type 2 diabetes	T-Coach® PSP (Sanofi)	To analyze baseline characteristics and changes in HbA1c and achievement of desired FPG levels, insulin dose and weight; and adherence and satisfaction to PSP program	<i>Clinical outcomes:</i> changes in HbA1c and FPG levels, insulin dose, and weight <i>PROs:</i> adherence to PSP satisfaction with PSP	93% achieved glycemic control. Significant changes in HbA1c and glycemic control and insulin dose at 6 months among those patients enrolled in PSP 42% patients discontinued PSP 9 out of 10 patients satisfied	Inconclusive	NA ^a
González Carrero et al., 2019 [17] (Spain)	Prospective study	Patients with diabetes	T-Coach® PSP (Sanofi)	To evaluate the evolution of the glycemic control of a patient with type 2 diabetes treated with insulin glargine U300 and enrolled at the T-Coach® platform	<i>Clinical outcomes:</i> improvement of diabetes control	T-Coach® platform improves the control of the diabetic patient	Yes	NA ^a

Table 3 (continued)

Author, year (country)	Type of observational study	Study population (size and disease)	PSP evaluated (funder)	Objective of the study	Outcomes evaluated in the study	Main results	Main objective achieved	STROBE
López Giménez and Checa, 2019 [16] (Spain)	Prospective comparative study	Patients with diabetes	T-Coach® PSP (Sanofi)	To assess glycemic control of a patient with type 2 diabetes treated with insulin glargine U300 and enrolled at T-Coach® platform	<i>Clinical outcomes:</i> glycemic control	Higher percentage achieving FBG goal in PSP cohort	Yes	NA ^a
Kohlmann et al., 2013 [24] (Germany)	Cross-sectional study and Internet survey	1123 adults with MS	BetaPlus PSP (Bayer)	To evaluate patients' needs and the PSP's role in meeting those needs	<i>PROs:</i> satisfaction with the PSP QoL	QoL: PCS and MCS scores were 45.5 and 45.8, respectively Highly satisfied (mean: 8.5 of 10)	Yes	19/22
Pozzilli et al., 2011 [11] (14 countries from Europe, Middle East, and Asia)	Prospective comparative study	1077 patients with MS	BetaPlus PSP (Bayer)	To assess the impact of elements of the PSP on adherence	<i>PROs:</i> treatment adherence	61.8% of patients adherent after 24 months Drivers: depression, QoL, and the use of autoinjector devices were predictors of adherence	Yes	19/22
Lyons et al., 2019 [21] (UK)	Retrospective study	133 patients with MS	Adveva® PSP (Merck)	To evaluate the impact of a proactive telephone-based PSP	<i>PROs:</i> adherence to treatment	98% of patients self-reported to have completed their first-year course as prescribed	Not clearly defined	NA ^a
Morgan et al., 2020 [20] (UK)	Retrospective study	133 patients with MS	Adveva® PSP (Merck Serono)	To evaluate the impact of a proactive telephone-based PSP	<i>PROs:</i> adherence to treatment	100% of patients self-reported adherence	Not clearly defined	NA ^a
Murthy et al., 2017 [28] (UK)	Patient case report	3 patients with non-Hodgkin lymphoma	You&i™ PSP (Janssen)	To assess patient satisfaction and evaluate if You&i™ program help to improve adherence and persistence to ibrutinib/YES	<i>PROs:</i> patient satisfaction	Patient 1: improvement in management of adverse effects Patient 2: improvement in educational support Patient 3: increase of compliance	Yes	6/22

Table 3 (continued)

Author, year (country)	Type of observational study	Study population (size and disease)	PSP evaluated (funder)	Objective of the study	Outcomes evaluated in the study	Main results	Main objective achieved	STROBE
NCT02750800 [15] (Hungary)	Prospective study. Model: case only	427 ADA-treated patients with various pathologies (RA; AS; PsA; Pso; CD; UC)	Abbvie Care 2.0 (Abbvie)	To evaluate the effectiveness of ADA plus AbbVie Care 2.0 PSP	<i>Clinical outcomes</i> PROs: QoL treatment satisfaction treatment adherence <i>Economic outcomes:</i> number of hospitalizations, amount of sick leave, number of outpatient visits	Data not published yet	Other (study without published results)	NA ^a
Ostor et al., 2018 [13] (UK)	Prospective comparative study	ADA-treated patients with RA	Abbvie Care 2.0 (Abbvie)	To estimate the incremental economic value associated with enrollment in the PSP	<i>Economic outcomes:</i> work productivity and cost savings	Decrease in work impairment Decrease in hospitalizations, specialist visits, and imaging tests Increase in work productivity	Yes	NA ^a
Ryan et al. 2018 [26] (France, Germany, Italy, Spain and the UK)	Cross-sectional comparative study	344 ADA-treated patients with Pso	Abbvie Care 2.0 (Abbvie)	To describe the usage of the PSP among adult ADA-treated patients with psoriasis in Europe and the associated impact on patient outcomes	<i>Clinical outcomes:</i> PGA and remission status	Higher percentage of remission (80.3% vs 60.5%) and PGA values (41% vs 21%) In PSP cohort	Yes	NA ^a

Table 3 (continued)

Author, year (country)	Type of observational study	Study population (size and disease)	PSP evaluated (funder)	Objective of the study	Outcomes evaluated in the study	Main results	Main objective achieved	STROBE
Ryan et al. 2019 [25] (France, Germany, Italy, Spain and the UK)	Cross-sectional comparative study	344 ADA-treated patients with Psoriasis	Abbvie Care 2.0 (Abbvie)	To characterize the associated impact of this PSP on outcomes among ADA-treated adults with psoriasis in Europe	<i>Clinical outcomes:</i> PASI and PGA <i>PROs:</i> satisfaction <i>Economic outcomes:</i> work impairment and presenteeism	Improvement of PGA values (41% vs 21%), decrease in severity of disease 66.7% vs 34.8%, higher treatment success: 93.4% vs 80.5% and remissions (80% vs 60%) in PSP cohort High treatment satisfaction Decrease in work impairment (3% vs 21%) and presenteeism (3% vs 17.9%) in PSP cohort	Yes	NA ^a
Van den Bosh et al. 2017 [12] (15 countries ^b)	Prospective comparative study	1,025 ADA-treated patients with AR	Abbvie Care 2.0 (Abbvie)	To examine the effectiveness of ADA on rheumatoid arthritis treatment course over time in the context of PSP utilization	<i>Clinical outcomes:</i> changes in DAS28, SDAL, CDAL, and ACR 20/50/70 responses rates <i>PROs:</i> treatment satisfaction	42.8% improved clinical outcomes Increase in convenience, global satisfaction, and other PROs Decrease in activity impairment	Yes	19/22
Nogués et al., 2014 [14] (Spain)	Prospective study	23,069 patients with osteoporosis	Teriparatide educational support program (Eli Lilly)	To assess PSP persistence with, and reasons for withdrawal; and satisfaction with the PSP	<i>Economic outcomes:</i> work productivity <i>PROs:</i> persistence to the PSP satisfaction with the PSP	Retention in the program was 90.8% at 3 months and 64.1% at 24 months 92% of patients were totally satisfied with PSP	Yes	18/22
Van Maren et al., 2019 [19] (the Netherlands)	Retrospective study	1573 patients with osteoporosis	Teriparatide educational support program (Eli Lilly)	Whether an EMSP increased persistence to PSP	<i>PROs:</i> persistence to medication	2-year treatment persistence: 78.4% of EMSP vs 71.6% of BSP	Yes	18/22

Table 3 (continued)

Author, year (country)	Type of observational study	Study population (size and disease)	PSP evaluated (funder)	Objective of the study	Outcomes evaluated in the study	Main results	Main objective achieved	STROBE
Rieckmann et al., 2019 [10] (Germany)	Prospective comparative study	368 patients with MS	RebiStar PSP (Merck Serono)	To evaluate patient adherence in patients using RebiSmart®	<i>Clinical outcomes:</i> improvement in the SDMT raw scores <i>PROs:</i> treatment adherence QoL <i>Economic outcomes:</i> hospitalizations, working disability due to MS, and co-medication	SDMT improved in patients with higher adherence QoL: MusiQoL were mostly stable throughout the study duration, except for a slight deterioration observed in the FSMC Mean quantitative adherence: 85.3%; mean qualitative adherence: 67.0% More MS-related visits to physicians among patients with high adherence	Yes	18/22
Simons et al., 2011 [9] (Germany)	Prospective comparative study	48 patients with colorectal and breast cancer	Pharmaceutical Care Program (Roche)	To investigate the effect of an intensified multidisciplinary pharmaceutical care program on the adherence of patients with cancer treated with capecitabine	<i>PROs:</i> daily and overall adherence to treatment	Increase in adherence in PSP cohort 97.9% vs 90%	Inconclusive	20/22

ACR 20/50/70 American College of Rheumatology, ADA adalimumab, EMSP educational and motivational support program, FBG fasting blood glucose, CDAI Crohn's Disease Activity Index, DAS28 Disease Activity Score 28, FSMC, HbA1c hemoglobin A1c, MCS mental component score, MS multiple sclerosis, NA not applied, OID optimal insulin dose, PASI Psoriasis Area and Severity Index, PCS physical component score, PGA Physician Global Assessment, PROs patient-reported outcomes, PSPs patient support programs, QoL quality of life, SDAI Simplified Disease Activity Index, SDMT Symbol Digit Modalities Test, STROBE Strengthening the Reporting of Observational Studies in Epidemiology

^aThe publication did not provide enough information to verify the STROBE checklist

evaluated the variations in impairment in the workplace; three of them used the Work Productivity and Activity Impairment Questionnaire [12, 13, 15], two used an ad hoc questionnaire on work capacity [10, 25], and one collected the amount of sick leave [15]. Second, three studies collected and analyzed the use of healthcare resources (hospitalizations and specialist visits, among others) [10, 13, 15].

According to the study results, proposed objectives were achieved in 75% of the studies ($n = 15$), demonstrating an increase in patients reported adherence and persistence [10–12, 14, 19], an improvement in patient satisfaction and/or quality of life [10, 11, 14, 22, 24, 25, 28], an improvement in clinical outcomes [10, 12, 16–18, 22, 23, 25, 26], and reductions in the costs associated with the use of healthcare resources [10, 12, 13, 25] (Fig. 2). Regarding the remaining publications ($n = 5$), 10% ($n = 2$) were inconclusive as it was not possible to assess whether participation in the PSP had induced an improvement in patients outcomes [9, 27], in another 10% ($n = 2$), the objective to achieve with the PSP was not clearly defined a priori [20, 21], and 5% ($n = 1$ publication) were an observational study report classified as others because no results had yet been published [15].

Results showed that overall, patients who participated in a PSP were very satisfied with the intervention. Most of them provided satisfaction scores varying from 8.5 to 9 (on a scale of 0–10) and would recommend its use to other patients (data not shown). Moreover, study results suggested that PSPs contributed to increase patients' adherence to medicines (adherence range from 61.8% to 98%), to improve clinical

measures (such as glycemic control in diabetes mellitus), and to reduce healthcare-associated costs (Fig. 2, Table 3).

4 Discussion

Patient support programs are becoming increasingly important as a service that provides support to the patient beyond the medication itself. The objectives of the PSPs vary according to the characteristics of the disease or the type of medication. Patient support programs can provide information and counseling to the patient for better disease management, include training or virtual reminders to improve patient adherence to medication, or provide patient education to identify potential side effects that need to be monitored.

The diversity of the characteristics of the PSPs evaluated, and the heterogeneity of the characteristics of the observational studies reflect the complexity of these disease-specific programs that are built ad hoc for specific diseases, treatments, and patients. The PSPs evaluated in this review were mostly based on supportive or educational interventions to help patients to understand and manage their symptoms. They comprised educational modules to inform and raise awareness [11–13, 15, 24–26, 28], patient monitoring services [11–13, 15, 24–26, 28], home delivery of medications [12–15, 19, 25, 26], and/or nurse home-visit services for treatment administration [11, 14, 19, 24].

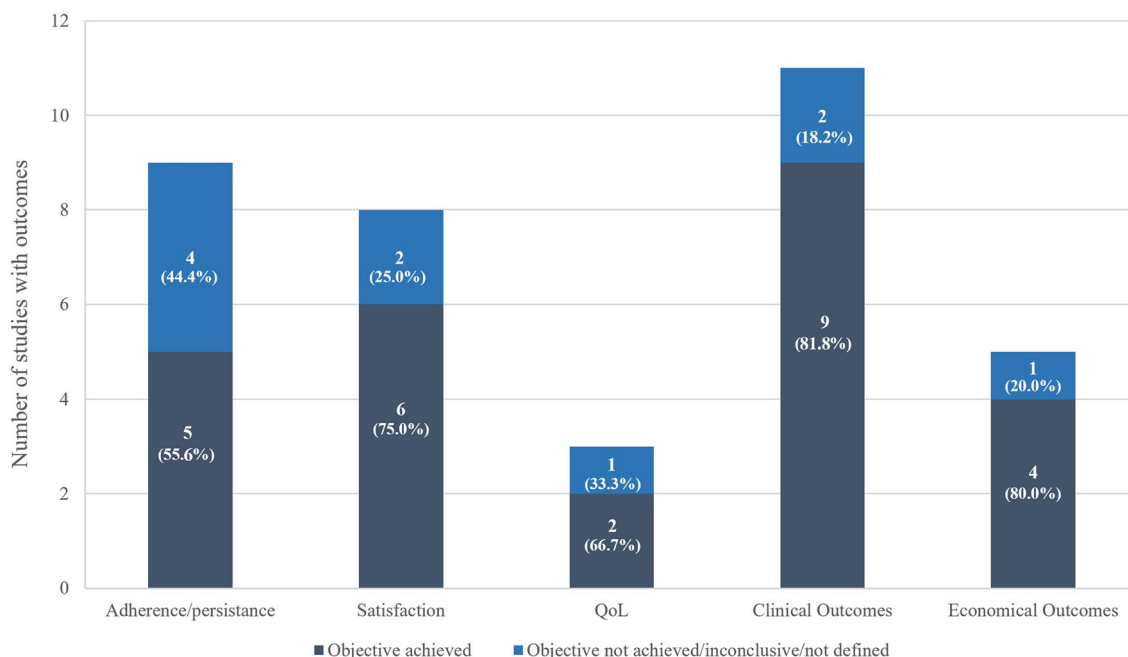


Fig. 2 Distribution of studies according to the type of outcomes reported and the achievement of the outcomes' objectives. *Objective not achieved includes inconclusive, not clearly defined a priori, and a study without published results. *QoL* quality of life

The results of the review provide an overview of the benefits of PSPs in terms of improved adherence, HRQoL gains, better clinical outcomes, and a reduction in the use of healthcare resources and associated costs. Overall, 75% of the studies claimed that the expected objectives were achieved after implementing the PSPs, in particular those involving clinical (80%) and economic outcomes (80%) and patient satisfaction (75%). These percentages are somehow higher than those reported by Ganguli et al. [1], where 64.1% of studies reported at least one significant positive clinical outcome and 64% reported a significantly positive humanistic outcome. This difference may be attributed either to the difference in PSP definitions or to a different way of assessing the achievement of the objective between the two studies. However, the heterogeneity in the studies appraised with respect to data collection timing (i.e., retrospective, prospective), comparison approaches (not existing vs existing), and the wide variety of instruments for the collection of evidence (scored surveys, ad hoc questionnaires, specific definitions, qualitative and quantitative measurements) make comparison between studies difficult. Moreover, because of a lack of a control arm in half of the reviewed studies, no conclusion can be drawn from the intervention groups that were compared to standard care. The inclusion of a control arm in future studies conducted to assess the impact of a PSP is highly recommended.

The heterogeneity observed in this review highlights the need to harmonize the definition, methods, and measurement of the effectiveness of PSPs. The application of new digital technologies and big data analysis will open up new opportunities to optimize and accelerate this process [29]. Validated initiatives such as the International Patient Decision Aids Standards, intended to help in the development of patient decision aids, the STROBE [8], which provides recommendations to improve the quality of reporting of observational studies or the systematic use of the PRISMA [5] as a quality standard for systematic literature reviews, may contribute to increase consistency, quality, and methodological rigor.

In addition to the lack of standards, the review also shows that the scarcity of patient safety data from PSPs prevents insight being gained into adverse events from a primary source [2], and therefore, the opportunity to ensure better risk management that would benefit the well-being of patients is lost [30]. Only one of the articles mentioned and discussed the adverse events reported during the study [10]. Additionally, none of the studies included in the review assessed a healthcare professional's perspective of the PSP. Therefore, an essential opinion needed to gain a complete multidisciplinary perspective [31] contributing to the suitability of methods and its future evolution is missing. Hence, potential improvements to be considered in the design of future studies to evaluate PSPs concern the introduction of

patient safety information and more involvement by healthcare professionals.

Therefore, there is a need to develop guidelines and recommendations to improve the framework for the evaluation of PSPs in Europe. This review may serve as a basis for providing recommendations for designing and implementing future PSP evaluation approaches that successfully meet the needs of patients, healthcare professionals, and regulatory authorities.

This literature review has several limitations. Some of these limitations relied on the search methods such as the databases searched because we did not include Embase or the search strategy, as we limited it to studies published in English or Spanish from 2010 onwards or conducted only in European countries. However, limiting our review to studies conducted in Europe is consistent with the study's approach, has allowed us far greater homogeneity among the PSPs evaluated, and has ensured that these PSPs are part of a common overarching regulatory framework (i.e., EMA).

Other limitations are related to the review studies' heterogeneity and the lack of control arms in half of them. Consequently, no conclusion could be drawn to determine if the interventions were superior to standard care.

5 Conclusions

The growing number of PSP-related publications in Europe during the last 10 years shows a growing interest in these self-management programs. As these initiatives may be promoted by different stakeholders other than the pharmaceutical industry, points to awareness regarding its relevance at different levels of action. Patient support programs may have an important role to play in improving the effectiveness of treatment, clinical outcomes, and patient satisfaction, especially in chronic diseases. However, in order to reach their full potential, the development of guidelines and recommendations to harmonize the definition of PSPs, standardize methods, systematically measure their impact, and develop and use new digital technologies should be a priority for the different stakeholders involved in their design and implementation.

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Declarations

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Ethics Approval Not applicable.

Consent to Participate Not applicable.

Consent for Publication Not applicable.

Availability of Data and Material The datasets generated and/or analyzed during the current review are available from the corresponding author on reasonable request.

Code Availability Not applicable.

Authors' Contributions JAS: conceptualization; methodology; supervision; roles/writing, original draft; writing, review, and editing; EA: conceptualization; data curation; formal analysis; methodology; roles/writing, original draft; writing, review, and editing; SDC: conceptualization; methodology; supervision; roles/writing, original draft; writing, review, and editing; MC: conceptualization; methodology; supervision; roles/writing, original draft; writing, review, and editing; LPC: data curation; formal analysis; methodology; roles/writing, original draft; writing, review, and editing; LL: conceptualization; methodology; supervision; roles/writing, original draft; writing, review, and editing.

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