



Higher Medication Adherence and Lower Opioid Use Among Individuals with Autoimmune Disease Enrolled in an Adalimumab Patient Support Program in the United States

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ABSTRACT

Introduction: Opioid use is prevalent among patients with autoimmune conditions, despite not being a recommended treatment. Tumor necrosis factor inhibitor (anti-TNF) therapy is an effective treatment for these autoimmune conditions, and patient support programs (PSPs) have been developed to help patients manage their prescribed treatments. This study was conducted to evaluate the impact of PSPs on

anti-TNF adherence and opioid use using data on adalimumab (ADA), an anti-TNF.

Methods: The study used insurance claims data linked to ADA PSP data on patients who initiated ADA after 01/2015, were commercially insured, and had data coverage for 1 year before and after (i.e., during the follow-up period) ADA initiation. Patients with opioid use in the 3 months before ADA initiation were excluded. PSP patients enrolled in the PSP within 30 days of ADA initiation and had 2+ PSP nurse ambassador interactions; non-PSP patients had no PSP engagement. ADA adherence [proportion of days covered (PDC), persistence], opioid initiation, 2+ opioid fills, and opioid supply during follow-up were compared between cohorts using regression models that controlled for patient characteristics.

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Results: Results were obtained for 1952 PSP and 728 non-PSP patients. PSP patients demonstrated better adherence to ADA than non-PSP patients, including higher PDC and persistence (all $p < 0.001$). PSP patients were 13% less likely to initiate opioids and 26% less likely to have at least 2 fills than non-PSP patients, and they had fewer days of opioid supply (all $p < 0.01$).

Conclusions: This study supports the benefit of PSPs and suggests that the ADA PSP is associated with improved adherence and potentially lower opioid use.

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Key Summary Points

Patient support programs (PSPs) have been developed to help patients better manage their disease and adherence to treatments.

This study assessed treatment adherence and opioid use among patients with autoimmune diseases treated with adalimumab (ADA), with patients who participated in a PSP considered separately from those who did not.

This study of the ADA PSP suggested that, although it did not target opioid use, patient participation in the PSP was associated with increased ADA adherence and lower rates of opioid initiation and use.

While further research is needed to understand the specific mechanisms for the impact of the ADA PSP, participation in the PSP may be associated with improved medication-taking behavior. This may lead to better autoimmune disease control and improved pain management strategies, which could reduce opioid use.

DIGITAL FEATURES

This article is published with digital features, including a summary slide to facilitate understanding of the article. To view digital features for this article go to <https://doi.org/10.6084/m9.figshare.14414768>.

INTRODUCTION

While opioids were initially restricted to treat acute and cancer pain, they have increasingly

been used to treat chronic noncancer pain since the late 1990s; studies have estimated the prevalence of opioid use in the United States (US) to range from 14 to 38% [1–3]. In 2017, the US Department of Health and Human Services declared a public health emergency to address the growing national opioid crisis [4]. In response to the opioid crisis, prescription drug monitoring programs have been implemented throughout the US to reduce opioid-related misuse, abuse, and mortality. However, there is a lack of consistent evidence regarding the effectiveness of these programs, possibly due to variations in study design and ease of program operability [5, 6].

The Centers for Disease Control and Prevention recommend that opioids not be considered first-line or routine therapy for chronic pain outside of active cancer, palliative, and end-of-life care [7]; however, the pain associated with chronic autoimmune conditions [e.g., rheumatoid arthritis (RA), psoriatic arthritis (PsA)] can warrant the use of opioids [8–11]. Tumor necrosis factor inhibitor (anti-TNF) therapy is an effective treatment for various autoimmune conditions [12, 13]. Previous studies have shown mild reductions in opioid use for patients with autoimmune conditions such as RA and Crohn's disease (CD) after anti-TNF therapy initiation [14–17]. As a result, patient support programs (PSPs) have been developed to help patients better manage their diseases and their adherence to treatment regimens, with the goal of improving health outcomes for a wide range of medications and diseases [18]. HUMIRA Complete, a PSP associated with the anti-TNF Humira [adalimumab (ADA)], includes financial assistance, engagement with a registered nurse for product education and support via a nurse ambassador program, provision of a sharps container and instructions for the disposal of used pens and syringes, medication reminders via calls, email, or text, an injection training program, and aid for traveling short distances with ADA. Eligible patients may opt into as many of these services as they choose, and participation is free for patients.

Previous studies showed that patients who enrolled in the HUMIRA Complete PSP had

improved refill adherence and persistence with ADA and reduced medical costs relative to patients who used ADA but did not join the PSP [19–25]. However, opioid use has not been previously investigated. This study characterized the impact of PSP enrollment and the product support offered through HUMIRA Complete on anti-TNF adherence and opioid use using claims data linked to data from the HUMIRA Complete PSP.

METHODS

Study Design and Data Sources

This longitudinal, retrospective cohort study used real-world claims data from the Symphony Health Solutions (SHS) administrative claims database (01/01/2006–10/31/2018), which was linked to Humira PSP data. The SHS database includes patient-level claims data, including medical and pharmacy claims, covering more than 280 million people in recent years and a variety of payers from a large, geographically diverse set of electronic claims processors across the US.

Records of PSP enrollment and program elements were collected via an integrated, coordinated care platform. Data were de-identified and linked to SHS administrative claims using pseudonymized patient tokens generated by a proprietary de-identification engine (Synoma, Symphony Health, Phoenix, Arizona, USA). Details of this method have been previously published [20]. Such linking provided a unique opportunity to evaluate how treatment use and patient outcomes are associated with PSP participation for the treatment of chronic diseases. Institutional review board approval was not required because de-identification was conducted before the SHS and PSP records were made available to researchers; no identifiable protected health information was accessible. Ethics board approval was not applicable to the conduct of this study. The current study had full permission to access and use the data from Symphony Health Solutions, which were provided under license.

Study Population

Eligibility Criteria

Patients were eligible for inclusion if they had initiated ADA treatment between 01/2015 and 10/2018 and were aged ≥ 18 years when initiating ADA. Patients were required to have ≥ 2 claims with a diagnosis for an autoimmune disease for which treatment with ADA was indicated [RA, PsA, ankylosing spondylitis (AS), CD, UC, plaque psoriasis (PS), hidradenitis suppurativa (HS), uveitis (UV)] on different days, with ≥ 1 occurring before ADA initiation. Patients were also required to have continuous data coverage during the entire study period. Patients were excluded if they had previously used any other anti-TNF treatment (i.e., etanercept, certolizumab pegol, golimumab, infliximab); all claims from 2006 until the patient's first ADA claim were considered to assess whether patients were anti-TNF naïve. Patients with government-provided insurance (e.g., Medicaid, Medicare) at ADA initiation were also excluded because they were ineligible for the PSP financial assistance component. Patients with any opioid use (identified using Generic Product Identifier 65-xx)¹ in the three months before ADA initiation were excluded, as these patients may have more severe pain and would have added heterogeneity to the sample (in sensitivity analyses, the opioid washout was extended to 6 months). The index date was defined as the date of the first ADA prescription drug claim. The baseline period was defined as the 12 months before the index date, and the follow-up period was defined as the 12 months after the index date (index date inclusive).

SHS Data Coverage

The SHS data did not include an enrollment or eligibility file. To ensure continuous data coverage for patients during the study period, algorithms based on the observed frequency of medical and drug claims were used. Patients were considered to have continuous medical data coverage if the interval between any two

¹ The most commonly prescribed opioids in the current study were hydrocodone (in combination with acetaminophen), tramadol, and oxycodone.

consecutive medical claims was no more than 120 days during the study period [24], and patients were considered to have continuous drug data coverage if they had at least one pharmacy claim in every quarter during the study period. Patients were required to meet both the continuous medical and drug data coverage criteria during the baseline and follow-up period included in the analysis.

Cohort Assignment

Patients who met the eligibility criteria were categorized into two cohorts based on their engagement with the PSP. The PSP cohort included patients who enrolled in the PSP within 30 days before or after the index date and engaged with the nurse ambassador program (i.e., participated in the initial call and ≥ 1 follow-up). The non-PSP cohort included patients who did not enroll in any component of the HUMIRA Complete PSP. Patients who did not meet the criteria of either cohort were excluded.

Outcomes

ADA Use Outcomes

The ADA use outcomes included the proportion of days covered (PDC) by ADA during the follow-up period; adherence, defined as PDC $\geq 80\%$; persistence, defined as not having discontinued ADA during the follow-up period; and days on ADA treatment. ADA PDC, adherence, and discontinuation were calculated using a previously published methodology [20]. Briefly, PDC was calculated as the sum of the number of days covered by the reported supply of ADA prescription drug claims divided by the total number of days in the 12-month follow-up period. Patients were considered to have discontinued ADA if they switched to another biologic or had an ADA treatment gap that exceeded the days of supply on their last ADA claim with no further ADA prescriptions during the follow-up period. Patients who did not discontinue were considered to have shown ADA treatment persistence.

Opioid Use Outcomes

The primary outcomes on opioid use assessed during the follow-up period were initiation of opioids (defined as having ≥ 1 opioid fill during the follow-up period) and the number of days of opioid supply (obtained from the pharmacy claims) among the subgroup of patients with opioid use in the follow-up period. Additional measures of the extent of opioid use included an indicator for having ≥ 2 opioid fills during the follow-up period and indicators for having > 15 , > 30 , > 60 , and > 90 days of opioid supply during the follow-up period.

Statistical Analyses

Descriptive statistics were used to summarize patient characteristics, as well as outcomes on ADA and opioid use during the follow-up period; continuous outcomes were described using means and binary outcomes using percentages. Statistical comparisons between cohorts were conducted using Wilcoxon rank-sum tests for continuous variables and chi-square tests for categorical variables. Generalized linear regression models were used to assess differences in outcomes between the PSP and non-PSP cohorts during the follow-up period, logistic regression models were used for binary outcome variables, while negative binomial regression models were used for count variables. Models for ADA use were adjusted for age, sex, Charlson Comorbidity Index (CCI) [26, 27], index autoimmune disease, and biologic-naïve status at index date (i.e., no previous use of any of the biologics in Table S1 in the electronic supplementary material). Models for opioid outcomes adjusted for the same set of baseline characteristics as well as opioid use during the baseline period (prior to 3 months before the index date). In sensitivity analyses, additional controls for patient income or for having cancer in the baseline period were added.

All analyses were conducted for the overall sample and for the following three indication groups: gastroenterological disorders (CD and UC), dermatological disorders (Ps and HS), and rheumatologic disorders (RA, PsA, and AS) and UV combined.

Statistical significance was based on a two-sided alpha error level of 0.05 in all analyses. All analyses were conducted using SAS Enterprise Guide version 7.1 (SAS Institute, Cary, NC, USA).

RESULTS

Sample

A total of 1952 patients met the inclusion criteria for the PSP cohort and 728 patients met the criteria for the non-PSP cohort (Fig. 1). Index and baseline characteristics are presented in Table 1. The mean ages of the PSP cohort and the non-PSP cohort were 51.0 and 51.4 years, respectively ($p = 0.29$); 71.2% of the PSP cohort and 65.9% of the non-PSP cohort were females ($p < 0.01$). The distribution of autoimmune diseases was relatively similar for both cohorts. However, patients in the PSP cohort were

slightly more likely to have CD or HS than non-PSP patients, while a slightly higher share of non-PSP patients had RA. The PSP cohort had a lower baseline CCI than the non-PSP cohort (0.8 vs. 1.1, $p < 0.01$), and the PSP cohort had a higher proportion of patients that were biologic naïve as of the index date (86.5% vs. 83.0%, $p < 0.05$).

ADA Adherence

Patients in the PSP cohort demonstrated significantly greater adherence to ADA than patients in the non-PSP cohort during the 12-month follow-up, as defined by PDC (62.5% vs. 46.9%, adjusted $p < 0.001$; Table 2) and persistence (44.8% vs. 29.4%, adjusted $p < 0.001$; Table 2). Patients in the PSP cohort remained on ADA treatment significantly longer than non-PSP patients; the mean number of days on ADA treatment was 23% longer

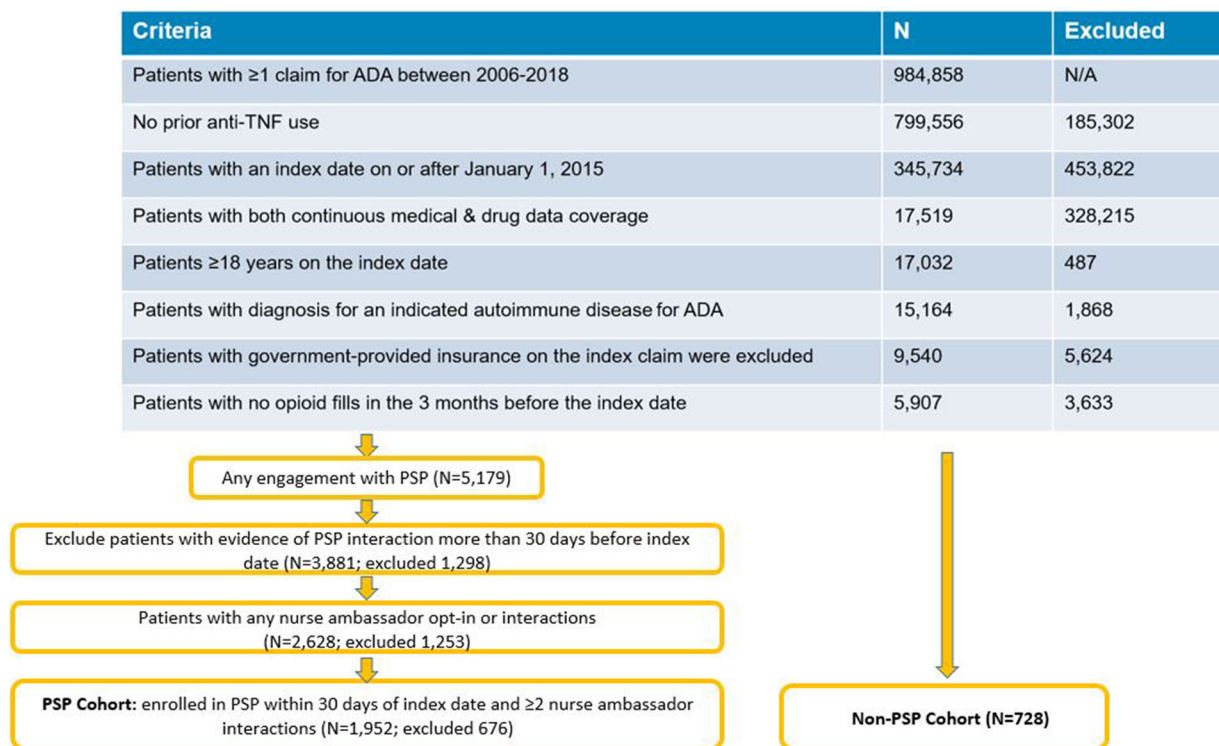


Fig. 1 Selection of the study population. ADA adalimumab, N/A not applicable, PSP patient support program, TNF tumor necrosis factor

Table 1 Patient characteristics

	PSP (<i>N</i> = 1952)	Non-PSP (<i>N</i> = 728)	<i>p</i> value ^a
Characteristics at index date			
Age (years), mean [SD]	51.0 [12.1]	51.4 [13.8]	0.2935
Female, <i>N</i> (%)	1390 (71.2%)	480 (65.9%)	0.0082*
Index autoimmune disease, ^b <i>N</i> (%)			
Rheumatoid arthritis	703 (36.0%)	308 (42.3%)	0.0028*
Psoriasis	338 (17.3%)	137 (18.8%)	0.3647
Crohn's disease	333 (17.1%)	74 (10.2%)	< 0.0001*
Ulcerative colitis	270 (13.8%)	86 (11.8%)	0.1708
Psoriatic arthritis	120 (6.1%)	55 (7.6%)	0.1896
Hidradenitis suppurativa	77 (3.9%)	16 (2.2%)	0.0280*
Uveitis (noninfectious)	63 (3.2%)	33 (4.5%)	0.1057
Ankylosing spondylitis	48 (2.5%)	19 (2.6%)	0.8239
Biologic naïve, ^c <i>N</i> (%)	1689 (86.5%)	604 (83.0%)	0.0197*
Comorbidities during the baseline period ^d			
CCI, mean [SD]	0.8 [1.0]	1.1 [1.2]	< 0.0001*
Baseline opioid use ^d			
Any opioid use during the baseline period, <i>N</i> (%)	709 (36.3%)	285 (39.1%)	0.1778
Opioid days of supply, mean [SD]	8.2 [23.9]	11.1 [29.8]	0.0786
≥ 2 opioid fills, <i>N</i> (%)	319 (16.3%)	137 (18.8%)	0.1291

CCI Charlson Comorbidity Index, SD standard deviation

^a Statistical comparisons between patients were conducted using Wilcoxon rank sum tests for continuous variables and chi-square tests for categorical variables

^b Index autoimmune disease was defined as the most frequent diagnosis prior to the index date among the autoimmune diseases for which ADA is indicated

^c Biologic naïve includes patients without any claim made at any time before the index date with a code for a biologic listed in Table S1 (see the electronic supplementary material)

^d CCI and opioid use were summarized during the baseline period (defined as the 1-year period before the index date)

for PSP than for non-PSP patients (248.2 vs. 191.5 days, adjusted $p < 0.001$; Table 2).

Opioid Use

During the 12-month follow-up, opioid use was significantly lower in the PSP cohort compared to the non-PSP cohort (Fig. 2a, b). Patients in the PSP cohort were 13% less likely to initiate

opioids compared to the non-PSP cohort (38.1% vs. 44.0%, adjusted $p < 0.01$), and were 26% less likely to have had at least two opioid fills during the follow-up period (18.9% vs. 25.5%, adjusted $p < 0.001$). Additionally, among patients with opioid use in the follow-up period (PSP: $N = 743$; non-PSP: $N = 320$), those in the PSP cohort used opioids less extensively, as defined by the number of days of opioid supply, than those in the non-PSP cohort (27.9 days vs.

Table 2 Adherence to and persistence with ADA

	PSP (<i>N</i> = 1952)	Non-PSP (<i>N</i> = 728)	<i>p</i> value ^a	Adjusted (PSP vs. non-PSP) ^b	
				OR/IRR (95% CI)	<i>p</i> value
ADA adherence, ^c <i>N</i> (%)	831 (42.6%)	185 (25.4%)	< 0.0001*	2.17 (1.79, 2.63)	< 0.0001*
PDC (%), mean [SD]	62.5 [31.6]	46.9 [33.3]	< 0.0001*	1.32 (1.25, 1.40)	< 0.0001*
ADA persistence, ^c <i>N</i> (%)	875 (44.8%)	214 (29.4%)	< 0.0001*	1.95 (1.62, 2.35)	< 0.0001*
Days on treatment, mean [SD]	248.2 [125.7]	191.5 [136.3]	< 0.0001*	1.29 (1.21, 1.37)	< 0.0001*

ADA adalimumab, PDC proportion of days covered, SD standard deviation, OR odds ratio, IRR incidence rate ratio

^a Continuous variables were compared between the PSP and non-PSP cohorts using Wilcoxon rank-sum tests, and categorical variables were compared between the cohorts using chi-square tests

^b For binary variables, logistic regression models were used to estimate odds ratios, 95% CIs, and associated *p* values. For continuous variables, negative binomial regression models were used to estimate incidence rate ratios, 95% CIs, and associated *p* values. Models were adjusted for age, sex, CCI, index autoimmune disease, and biologic-naïve status

^c Adherence to and persistence with ADA were measured from the patient's first ADA claim (on the index date) until the end of the follow-up period. Patients were considered adherent if they had PDC \geq 80% and persistent if they did not discontinue during the follow-up period

37.3 days, adjusted $p < 0.01$). The PSP cohort was also less likely to use opioids for extended periods of time, with smaller percentages of PSP patients having > 15, > 30, > 60, or > 90 days of opioid supply during the 12-month follow-up period (Fig. 3; all adjusted $p < 0.05$). The results did not change (data not shown) in sensitivity analyses that included controlling for baseline cancer (as a means of capturing pain for which opioid use may be recommended) and controlling for patient income as an additional patient characteristic. In sensitivity analyses where the patient inclusion criteria were changed to require no opioid fills in the 6 months before initiating ADA, results were similar to the overall findings (data not shown).

The results by disease category are directionally consistent with the overall findings in that the proportion of patients initiating opioids and the extent of use are lower for the PSP cohort relative to the non-PSP cohort (Table S2 in the electronic supplementary material). However, some of the results lose statistical significance. For patients with gastroenterological disorders (CD and UC, *N* = 763), 40.0% of patients in the PSP cohort and 48.1% of patients in the non-PSP cohort initiated opioids during the follow-up period (adjusted $p < 0.05$). For

patients with dermatological disorders (PS and HS, *N* = 568), 38.6% of patients in the PSP cohort and 43.8% of patients in the non-PSP cohort initiated opioids during the follow-up period (adjusted $p = 0.17$). For patients with rheumatologic disorders (RA, PsA, AS) and UV (*N* = 1349 in total), 36.6% of patients in the PSP cohort and 42.4% of patients in the non-PSP cohort initiated opioids during the follow-up period (adjusted $p = 0.12$). Similarly, the mean number of days of opioid supply among patients with opioid use was numerically lower for the PSP cohort relative to the non-PSP cohort for all indications (gastroenterological: 20.6 vs. 32.0, adjusted $p = 0.89$; dermatological: 26.5 vs. 35.0, adjusted $p = 0.10$; rheumatologic and UV: 33.6 vs. 40.5, adjusted $p < 0.05$).

DISCUSSION

Opioid use is a pressing concern in the US, and is now considered a public health emergency [4]. The prevalence of opioid use is high among the general population and even more so among patients with autoimmune conditions [1–3], despite opioid analgesics not being a recommended treatment for these patients [7]. Given the reported risks associated with opioid

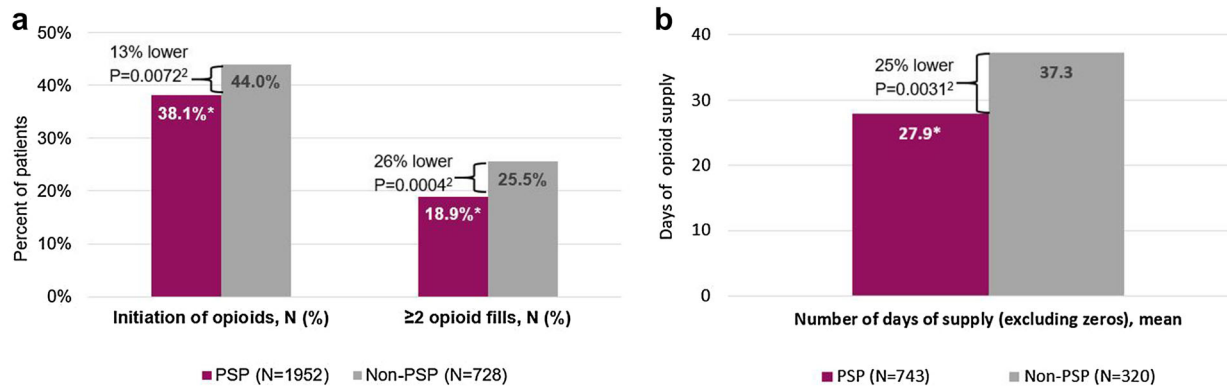


Fig. 2 **a** Initiation of opioids¹ during follow-up. **b** Days of opioid supply during follow-up. *PSP* patient support program. * $p < 0.05$ in the unadjusted model. ¹ Initiation of opioids was defined as having any opioid fills during the follow-up period. Mean days of opioid supply among patients who initiated opioids during the follow-up period were reported. The proportions and means presented in the figure are raw, unadjusted values. ² Adjusted p values

were estimated using multivariable regression models adjusting for age, sex, Charlson Comorbidity Index, index autoimmune disease, bionaiété at index date, and the baseline value of the outcome variable (e.g., for the regression of at least two opioid fills during the follow-up period, the regression controlled for having at least two opioid fills during the baseline)

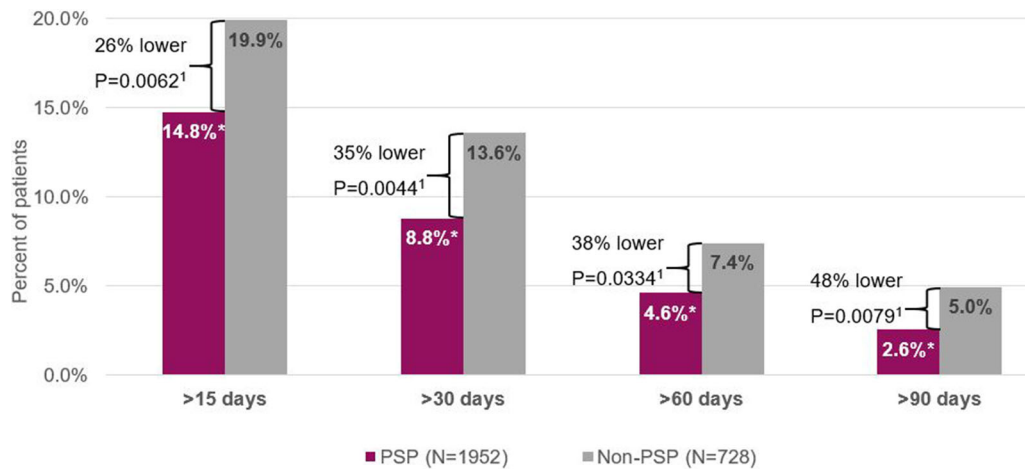


Fig. 3 Days of opioid of supply during follow-up. *PSP* patient support program. Proportions presented are raw, unadjusted values; * indicates $p < 0.05$ in unadjusted model. ¹ Adjusted p values were estimated using multi-variable logistic regression models adjusting for age, sex, Charlson Comorbidity Index, index autoimmune disease,

bionaiété at index date, and the baseline value of the outcome variable (e.g., for the regression of at least 15 days of opioid supply during the follow-up period, the regression controlled for having at least 15 days of opioid supply during the baseline)

use, it is vital to help patients reduce their risk for extended use [7, 28]. In this study, participation in the *PSP* was associated with lower rates of opioid initiation and a lower extent of opioid use following *ADA* initiation. The opioid

results observed in this study may result from better disease control due to improved *ADA* adherence. Consistent with prior studies [20–22, 24, 25], this study provides evidence that patients who participate in the *PSP*

demonstrate significantly greater adherence to, persistence with, and days on ADA treatment compared to patients in the non-PSP cohort. Biologics have been associated with significant improvements in pain, particularly when taken as prescribed [29, 30]. With better autoimmune disease control and improved pain management strategies, opioid use may be reduced [31]. Indeed, the improved ADA adherence observed for the PSP cohort in this study may lead to better underlying disease control, resulting in less pain and therefore less of a need for opioid use.

A potential explanation for the decrease in opioid use associated with PSP participation is adequate support. Patients enrolled in the PSP have access to nurse ambassadors, who provide product education and support related to prescribed treatment management; however, these nurses do not provide clinical information to patients, so this is unlikely to explain the opioid results. Contact with the nurse ambassadors may provide cognitive support and motivate patients to improve their own health literacy and increase their awareness of their own disease and treatment; these better-informed patients may be driven to avoid opioids, which are associated with negative consequences, and to seek alternative pain-management strategies.

Various programs have been implemented to limit opioid use, and have found limited success [5, 6]. While the ADA PSP did not target opioid use, the current study provides evidence that participation in the PSP is associated with improved ADA medication-taking behavior, which may result in lower rates of opioid initiation, providing additional evidence of the real-world benefit of PSPs. Other mechanisms, including improved health and disease education, may contribute as well.

This study has several limitations that should be noted. First, because patients choose whether or not to participate in the PSP, there are likely inherent differences between patients in the PSP and non-PSP cohorts; the study design mitigates the impact of these differences by controlling for observed patient characteristics in the statistical analyses, but may not be able to fully control for all of the relevant patient factors that impact both their decision

to join the PSP and their extent of opioid use. The indications for which opioids were prescribed are not observable. Accordingly, a sensitivity analysis that controlled for whether the patient had a diagnosis for cancer in the baseline period was conducted (since patients may use opioids to help control cancer-related pain), but the results did not change.

This study may also be limited in its generalizability to other patient populations or PSPs. It focused on patients who were not already dependent on opioids, defined as patients with no opioid use in the 3 months before initiating ADA. It also excluded patients who used government-provided insurance (e.g., Medicare, Medicaid), since they are not eligible to use the full set of services provided by the PSP. Other limitations are common in studies using SHS data, including the lack of an eligibility file and an inability to observe medications not filled through insurance. Consistent with previous research [20], algorithms were used to identify patients with medical and pharmacy coverage; however, some healthcare resource use may not have been captured and ADA adherence or opioid use may have been underestimated. However, this is unlikely to have differentially impacted the PSP and non-PSP cohorts or to have biased comparisons of cohorts. Finally, patients in this study may have participated in other unobserved assistance programs that could have improved their outcomes. The direction of the impact of such participation is uncertain. The study also does not focus on the different components of the PSP or on varying levels of engagement with the PSP.

The design and results of this study suggest areas of interest for future research. Further research is needed to better understand the impact of PSPs on patients already using opioids. Another population of interest is patients who use government-provided insurance, since the components of the PSP that are available to them are limited, so they may present different results than those observed in the current study. Additional studies to better understand the mechanisms driving the results (e.g., increased treatment adherence, resulting in better disease control; increased health literacy; greater

motivation) may improve programs focused on reducing opioid use.

CONCLUSIONS

This study adds to the growing body of evidence on the impact of PSPs on patient treatment management by examining a previously unstudied outcome: opioid use among autoimmune patients, a pressing public health issue. We find that participation in the PSP is associated with increased ADA adherence, lower rates of opioid initiation, and, among those who did initiate, a lower extent of opioid use. While further research is needed to understand the specific mechanisms behind these results, they point to the potential benefits of improved medication-taking behavior and better disease control that may be brought on by PSP participation.

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Compliance with Ethics Guidelines. Ethics board approval was not applicable to the conduct of this study. The current study had full permission to access and use the data from Symphony Health Solutions, which were provided under license.

Data Availability. The datasets generated during and/or analyzed during the current study are not publicly available due to the fact that the data are available from Symphony

Health Solutions but restrictions apply to the availability of these data, which were used under license for the current study. Data at the aggregate level are however available from the authors upon reasonable request and with permission of Symphony Health Solutions.

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