Reduced Healthcare Resource Utilization in Patients with Opioid Use Disorder in the 12 Months After Initiation of a Prescription Digital Therapeutic

Fulton F. Velez · Kathryn P. Anastassopoulos · Samuel Colman ·

Neel Shah · Laura Kauffman · Sean M. Murphy · Charles Ruetsch ·

Yuri A. Maricich

ABSTRACT

Background and Aims: reSET-O, an FDA-authorized prescription digital therapeutic (PDT) delivering cognitive behavioral therapy and contingency management to patients with opioid u®se disorder (OUD), may help improve clinical outcomes. One-year differences in healthcare resource utilization (HCRU) and costs post-PDT initiation were evaluated.

Methods: Retrospective analysis of healthcare claims data compared all-cause HCRU (across hospital facility encounters [sum of inpatient stays, treat-and-release emergency department [ED] visits, partial hospitalizations, and hospital outpatient department visits] and clinician services [procedure categories]) after PDT initiation (index) between reSET-O patients and controls. Overall and Medicaid-specific differences in HCRU, costs, and buprenorphine adherence were evaluated.

Findings: Cohorts included 901 reSET-O patients (median age 36 years, 62.4% female, 73.9% Medicaid) and 978 controls (median age 38 years, 51.1% female, 65.4% Medicaid). Compared to the control group, the reSET-O group experienced 12% fewer total unique hospital encounters (non-significant), driven by 28% fewer inpatient stays (IRR 0.72; 95% CI 0.55–0.96; $P = 0.02$), 56% fewer hospital readmissions [IRR 0.44; 95% CI 0.20–0.93; $P = 0.033$]), and 7% fewer ED visits (IRR 0.93; 95% CI 0.79–1.09; $P = 0.386$). Total clinician services increased by 1391 events versus controls. Differences were greater among the Medicaid patients. Adjustment for

F. F. Velez (✉) · N. Shah · Y. A. Maricich
Pear Therapeutics (US), Inc., 200 State St., Boston, MA 02109, USA
e-mail: fulton.velez@peartherapeutics.comN. Shah
e-mail: neel.shah@peartherapeutics.com
Y. A. Maricich
e-mail:
yuri.maricich@peartherapeutics.com

K. P. Anastassopoulos · S. Colman · L. Kauffman
Market Access Consulting, Labcorp Drug Development, Gaithersburg, MD, USA
K. P. Anastassopoulos
e-mail: kathryn.anastassopoulos@labcorp.com

S. Colman
e-mail:
sam.colman@labcorp.comL. Kauffman
e-mail: Laura.Kauffman@labcorp.com

S. M. Murphy
Department of Population Health Sciences, Weill Cornell Medical College, New York, NY, USA
e-mail: smm2010@med.cornell.edu

C. Ruetsch
Health Analytics, Columbia, MD, USA
e-mail: c.ruetsch@healthanalytics.com

concomitant baseline substance use and mental health disorders resulted in similar HCRU incidence rate ratios. Changes in all-cause HCRU drove per-patient per-year cost differences of − $2791 versus controls (− $3832 versus Medicaid controls). Adjusted mean medication possession ratio was 0.848 (SE 0.0118) at 12 months for reSET-O patients, which was significantly higher than controls (0.761 [SE 0.0108]; $P < 0.001$).

Conclusions: Use of reSET-O is associated with significant and durable real-world reductions in ED and inpatient (including readmissions) utilization, reduced net costs, and increased clinician services and buprenorphine adherence. Differences in costs versus controls were greatest among Medicaid patients.

Infographic:

Reduced Healthcare Resource Utilization (HCRU) in Patients With Opioid Use Disorder (OUD) in the 12 Months After Initiation of a Prescription Digital Therapeutic (PDT)

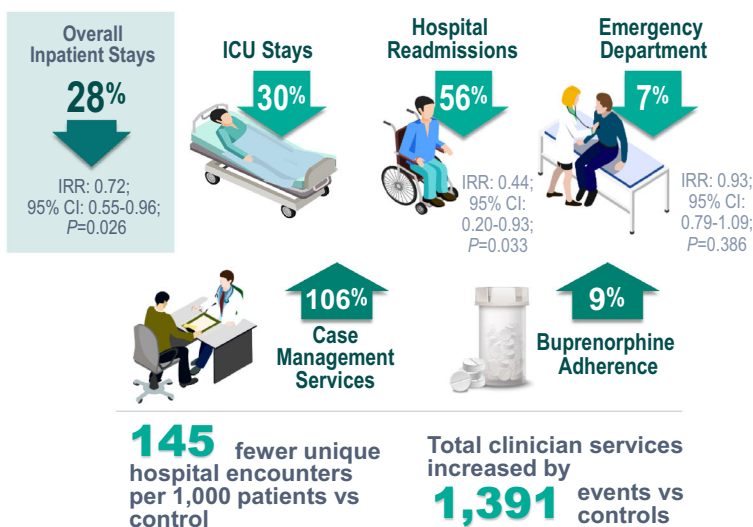FF Velez, K Anastassopoulos, S Colman, N Shah, L Kauffman, SM Murphy, C Ruetsch, YA Maricich. 2022

reSET-O®, an **FDA-authorized PDT**, delivering cognitive behavioral therapy and contingency management to patients with opioid use disorder (OUD) may help improve clinical outcomes.

One-year differences in HCRU showed decreased costs with post-PDT initiation.

Use of reSET-O is associated with **significant and durable** real-world reductions in emergency department (ED) and inpatient (including readmissions) utilization, reduced net costs, and increased buprenorphine adherence. Differences in costs vs controls were greatest for Medicaid.

Real-world 12-month Impact on HCRU
reSET-O® (n=901)[1] vs Control (n=978)[2]

Overall Inpatient Stays
28%
IRR: 0.72; 95% CI: 0.55-0.96; *P*=0.026

ICU Stays
30%

Hospital Readmissions
56%
IRR: 0.44; 95% CI: 0.20-0.93; *P*=0.033

Emergency Department
7%
IRR: 0.93; 95% CI: 0.79-1.09; *P*=0.386

Case Management Services
106%

Buprenorphine Adherence
9%

145 fewer unique hospital encounters per 1,000 patients vs control

Total clinician services increased by **1,391** events vs controls

Changes in all-cause HCRU drove per-patient per-year cost differences of **-$2,791** versus controls (**-$3,832** versus Medicaid controls).

Methods: Retrospective analysis of healthcare claims data compared all-cause HCRU (across hospital facility encounters [sum of inpatient stays, treat-and-release emergency department [ED] visits, partial hospitalizations, and hospital outpatient department visits] and clinician services [all-observed CPT codes]) after PDT initiation between reSET-O patients and controls. Overall and Medicaid-specific differences in HCRU, costs, and buprenorphine adherence were evaluated.

Key Summary Points

Why carry out this study?

Opioid use disorder (OUD) continues to place a heavy cost burden on healthcare systems and society at large. Many patients suffer from chronic OUD and incur avoidable healthcare resource use and costs.

Many barriers to effective treatment of OUD may be overcome with prescription digital therapeutics (PDTs) delivering evidence-based, FDA-approved treatments to patients via mobile devices.

This study evaluated the real-world 12-month impact on healthcare resource utilization (HCRU) by comparing 901 patients with OUD treated with the reSET-O® PDT to 978 patients who were not treated with the PDT.

What was learned from this study?

Compared to controls, in the 12 months after treatment with the PDT, patients in the reSET-O group had significantly fewer inpatient stays as well as lower rates of overall hospital encounters, partial hospitalizations, and emergency department visits.

12-month per-patient costs related to fewer facility encounters were − $2791 lower compared to controls, with even lower costs per Medicaid patient (− $3832).

DIGITAL FEATURES

This article is published with digital features, including an summary infographic, to facilitate understanding of the article. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.20013323.

INTRODUCTION

According to the Centers for Disease Control and Prevention, three successive waves of overdose deaths associated with both licit and illicit opioid use have impacted the USA in recent decades [1]. The first wave began in the 1990s when prescriptions for opioid analgesics rose sharply. A second wave began around 2010 when increasing deaths from heroin use reached epidemic levels. The third wave began in 2013 with a rise in overdose deaths attributed to synthetic opioids, particularly illicit fentanyl and carfentanyl. This third wave continues to grow and is now morphing into a so-called fourth wave, with synthetic opioids being mixed into stimulants (such as methamphetamine and cocaine) and other counterfeit pills, the use of which is accelerating at a rate higher than that of unmixed opioids [2]. Deaths have continued to climb in recent years, and according to the latest reports 74,754 adults died as a result of opioid-related overdoses in the 12 months ending September 2021, representing an average of 205 deaths daily (Fig. 1) [3], a 55% increase since September 2019 [4]. Opioid-related overdoses now account for 75% of fatal overdoses for all substances, up from 70.6% in 2019, with synthetic opioids accounting for 86.6% of opioid-related deaths [4].

Fatal overdoses, however, represent just a small percentage of the total number of overdoses associated with use of opioids [5] and the total burden on society. Those suffering from long-term opioid use disorder (OUD), and those overdosing, are increasing avoidable healthcare spending, particularly that related to emergency department (ED) visits and inpatient stays [6]. Studies have shown that approximately eight out of ten overdose victims report at least one post-overdose sequela including falls, burns,

12 Month-ending Provisional Number of Drug Overdose Deaths by Drug or Drug Class
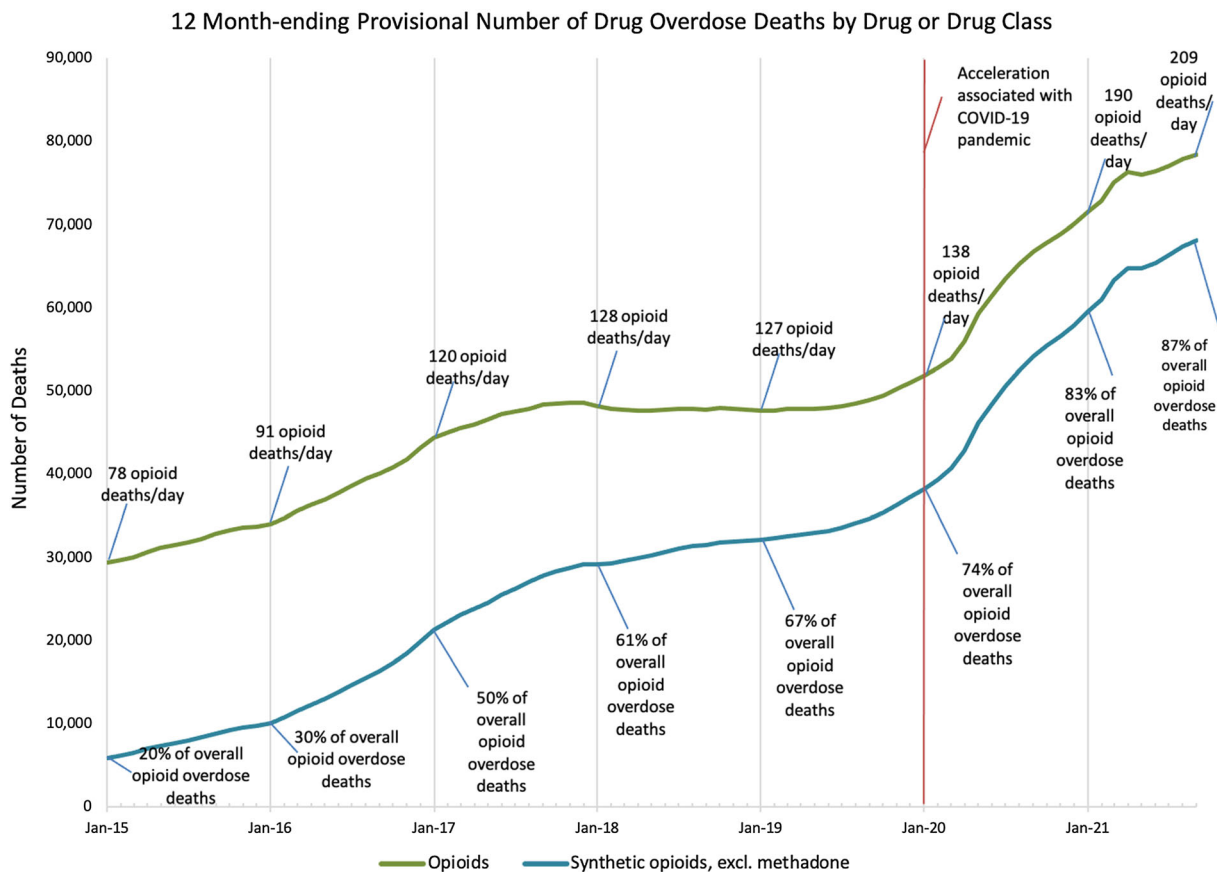
Fig. 1 Drug overdose deaths by drug or drug class. Overdose deaths have accelerated since the advent of the COVID-19 pandemic and are now at record levels. Created using CDC overdose data (CSV file) available at https://www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm (accessed 3/9/22)

assault while unconscious, chest infections, peripheral neuropathy, rhabdomyolysis, pulmonary edema, temporary limb paralysis, seizure, and cardiac arrhythmia [6]. These sequelae required hospital treatment in 33% of patients and admission in 14% [6]. Conversely, recent studies have shown reduced rates of acute care services when patients receive treatment, and that relationship is stronger with increased intensity of treatment and with increased adherence to medications for opioid use disorder (MOUD) (i.e., buprenorphine, methadone, or naltrexone) [7–9].

Medications and behavioral therapies are the gold standard treatments for OUD [10]. Medications for OUD work by reducing cravings for opioids, thereby reducing opioid use and its associated health risks [11], while behavioral

therapies such as cognitive behavioral therapy (CBT) and contingency management (CM) work by helping patients adopt successful substance avoidance behaviors, achieve greater control over personal, social, and vocational aspects of their lives, and increase retention in treatment [12]. The use of both treatments has been shown to reduce OUD-related costs [7, 8, 13]. A 2016 study by Moore et al. showed that CBT plus physician management with buprenorphine treatment can improve treatment outcomes, including opioid abstinence, compared to treatment without CBT [14]. Retention in treatment helps prevent a return to opioid use (including exposure to more potent synthetic opioids) and its increased risk of accidental overdose (fatal and non-fatal) due to loss of tolerance [11]. However, the provision of

supportive services to patients in recovery is hampered by a shortage of trained or certified providers, which led the National Institute on Drug Abuse to call for the development of digital versions of CBT for addictive disorders [15].

reSET-O® was authorized by the US Food and Drug Administration (FDA) in 2018 for patients with OUD being treated with buprenorphine. It is an 84-day (12-week) prescription digital therapeutic (PDT) [16] that delivers behavioral therapy based on the community reinforcement approach, an OUD-specific form of CBT. The clinical trials supporting FDA approval of reSET-O showed significantly increased levels of treatment retention and abstinence among patients using reSET-O compared to those receiving only buprenorphine [12, 17, 18]. Previous analyses have also shown that patients prescribed reSET-O engaged with treatment and had outcomes consistent with prior clinical trials [19], and that treated patients incurred reduced costs to third-party payers (for all healthcare resource use over 9 months) compared to controls, attributed mostly to a reduction in inpatient, intensive care unit (ICU), and ED visits, despite similar levels of buprenorphine adherence [20].

The current study sought to assess long-term (12 months post-treatment initiation) changes in healthcare resource utilization (HCRU), associated costs, and buprenorphine adherence in a large, all-comer population of patients who were prescribed reSET-O in real-world conditions.

METHODS

Data Source and Study Population

A retrospective 12-month, real-world analysis using HealthVerity PrivateSource20 claims data (from January 1, 2018 to February 28, 2021) was conducted. The data source includes closed medical and pharmacy claims for approximately 70 million commercial, 60 million Medicaid, and 15 million Medicare enrollees represented across 150 payers since 2015. Included were all adults prescribed reSET-O with available claims data, with at least 8 months of medical eligibility after reSET-O initiation (index date). A total of 901 patients in recovery from OUD who filled their prescription and engaged with the therapeutic were compared to a cohort of 978 patients in recovery from OUD who did not fill their prescription (Fig. 2). Changes in buprenorphine adherence
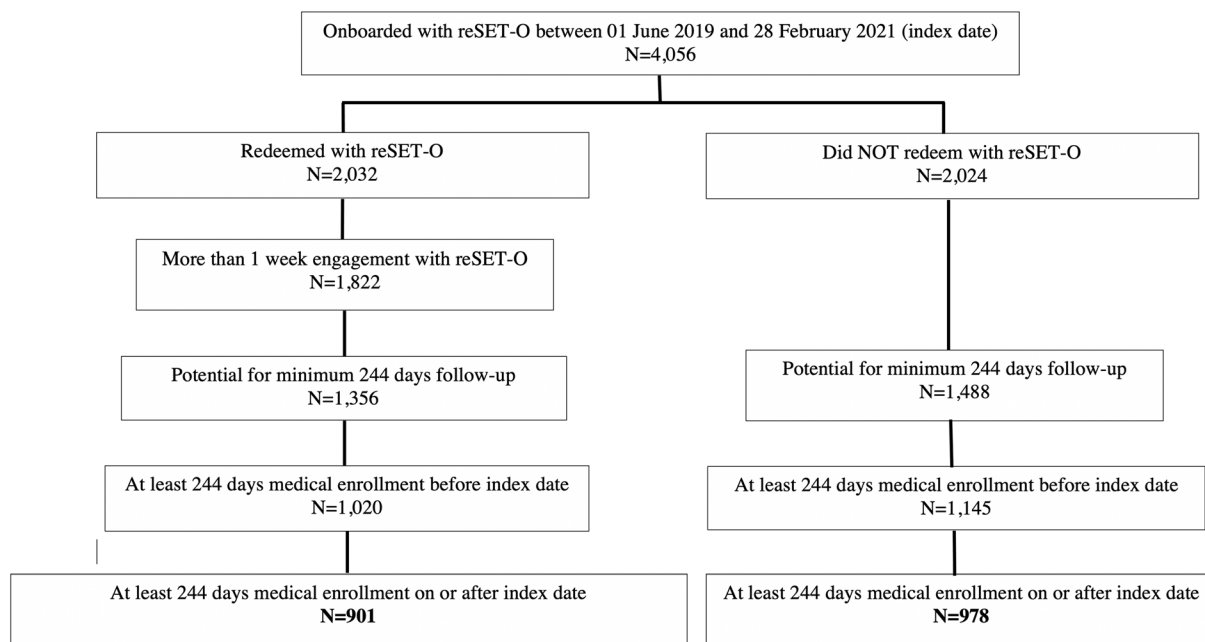
Fig. 2 CONSORT diagram of patient accrual

were also assessed. Index dates included January 10, 2019 through June 30, 2020. This study received a waiver of authorization for the use and disclosure of protected health information and a determination of exempt status under 45 CFR § 46.104(d)(4) from Western Institutional Review Board on October 13, 2021.

Study Measures

Claims were identified as hospital facility encounter claims or clinician services claims in order to characterize patients' HCRU. Hospital facility encounters included inpatient stays (within which intensive care unit [ICU] stays and hospital readmissions were separately assessed), ED visits (not admitted), partial hospitalizations (PH—defined as outpatient programs specifically designed for the diagnosis or active treatment of serious mental disorders where the patient receives care during the day and returns to a private residence at night), and hospital outpatient department (HOPD) visits. The composite outcome of unique hospital encounters (inpatient stays + PH + ED visits + HOPD visits) was also examined.

Clinician services included categories of Current Procedure Terminology (CPT) codes identified from clinician claims such as evaluation and management (E&M) codes, medical codes (e.g., cardiovascular, psychiatry, neurology), pathology and laboratory, and rehabilitative services. Lastly, buprenorphine adherence was evaluated using buprenorphine pharmacy claims.

Analyses

Patients who initiated reSET-O and engaged with the PDT for more than 1 week were included in the reSET-O cohort (index date is date of reSET-O initiation), and patients who were prescribed reSET-O but did not initiate it were included in the control cohort (index date is date of reSET-O prescription). Analyses included a comparison of all-cause HCRU between the 12-month post-index periods of the reSET-O cohort and the control cohort.

HCRU incidence rates and incidence rate ratios (IRRs) were calculated using a negative binomial model of counts of HCRU adjusted for age, sex, region, payer type, Charlson comorbidity index (CCI), and count of same HCRU, with an offset for the number eligible days in the post-index period. A further analysis adjusting for mental health and substance use disorders in the pre-index period was also performed. Mental health disorders included the following: anxiety, bipolar and related, depressive, disruptive, dissociative, eating, neurocognitive, neurodevelopmental, obsessive–compulsive, personality, schizophrenia, sleep, and somatic symptom. Substance use disorders included the following with an ICD-10 diagnosis claim for abuse, use, or dependence: cannabis, cocaine, hallucinogen, nicotine, sedative/hypnotic/anxiolytic, other psychoactive, and other stimulant.

Number of events were reported per 1000 treated patients to account for the difference in sample sizes between comparison groups. Buprenorphine adherence was also assessed and compared between the two cohorts with a linear model of the medication possession ratio (MPR) on cohort and eligible days in the post-index period [21]. MPR is calculated as the number of days' supply of buprenorphine during the post-index period divided by the number of eligible days in the post-index period. Adjusted MPR is derived from the least square means from a linear model of MPR on cohort and eligible days in the post-index period.

A scenario analysis of the cost impact of changes in facility and clinical service encounters was conducted using published per-patient facility costs for individuals with OUD: $19,023 for inpatient stays [22], $124,419 for ICU stays [23], $1,969 for ED visits [24], and 2020 Medicare reimbursement rates for remaining facility and clinician services, as has been performed in previous analyses [23].

Analyses were performed using SAS statistical software version 9.2 (SAS Institute Inc., Cary, North Carolina, USA) using paired t tests with $P < 0.05$ considered significant. Given the multiple tests conducted across the multiple HCRU categories, the false discovery rate (FDR) was used to assess statistical significance at

alpha of 0.05 for hospital facility encounters and clinician services.

RESULTS

There were some differences in the demographic and clinical characteristics between the reSET-O cohort ($N = 901$) and the control cohort ($N = 978$) (Table 1). The reSET-O patients were slightly younger (37.9 vs. 39.2; $P = 0.004$) with a greater percentage of female patients (62.4% vs. 55.1%; $P = 0.001$) and greater percentage of Medicaid patients (73.9% vs. 65.4%; $P = 0.001$). There was no difference in the mean Charlson comorbidity score ($P = 0.457$) or the percentage of patients with a mental health disorder ($P = 0.556$) or a substance use disorder ($P = 0.368$). There was also no difference in the percentage of patients with at least one buprenorphine prescription in the pre-index period ($P = 0.133$), and pre-index MPR was similar in both cohorts (reSET-O: 0.650; controls: 0.632; $P = 0.345$).

Table 2 shows differences in hospital facility encounters between the reSET-O and control cohorts. In the 12-month post-index period, inpatient stays showed the largest difference in number of events versus controls with a 28% lower incidence (IRR 0.72; 95% CI 0.55–0.96; $P = 0.026$; 49 fewer/1000 patients), and included a 30% decrease in ICU stays (11 fewer events/1000), and a 56% decrease in hospital readmissions (15 fewer events/1000). ED visits showed the second-largest difference versus controls, a 7% lower incidence (IRR 0.93; 95% CI 0.79–1.09; $P = 0.386$; 45 fewer events/1000 patients). The incidence of overall unique hospital facility encounters was 12% lower in the reSET-O cohort than in the control cohort (IRR 0.88; 95% CI 0.75–1.03; $P = 0.105$). Partial hospitalizations were reduced by 65 events/1000, although the binomial model could not be fit because of the small number of events, and HOPD visits had one additional event per 1000 patients representing a 6% increase. After FDR adjustment, inpatient stays and hospital readmissions were no longer statistically significant when compared to the FDR critical values of 0.008 and 0.017, respectively.

The clinician services categories with the largest difference in event counts between reSET-O and controls were E&M case management (106% increase; 953 additional events, IRR 2.06; 95% CI 1.57–2.71; $P < 0.001$), pathology and laboratory: drug assay (19% reduction; 944 fewer events; IRR 0.81; 95% CI 0.72–0.92; $P = 0.001$), psychiatry (23% increase; 789 additional events; IRR 1.23; 95% CI 1.02–1.48; $P = 0.029$); E&M outpatient visits (5% increase; 710 additional events; IRR 1.05; 95% CI 0.96–1.14; $P = 0.327$), and alcohol & drug abuse: self-help/peer services (39% increase; 395 additional events; IRR 1.39; 95% CI 0.94–2.05; $P = 0.095$). Among the next ten categories with the largest difference in event counts only two were statistically significant (E&M care plan, and surgery), although all showed a large difference in events: E&M hospital inpatient services (344 fewer events), alcohol and drug abuse: assessment (332 additional events), alcohol & drug abuse: crisis intervention (314 additional events), E&M care plan oversight (242 fewer events), alcohol & drug abuse: detox, inpatient (205 fewer events), alcohol & drug abuse: behavioral health, residential treatment program (197 fewer events), surgery (171 additional events), E&M: partial hospitalization services (171 fewer events), pathology and laboratory: drug assay, before opioid treatment (161 additional events), pathology and laboratory: other (151 fewer events). Overall there were 1391 additional clinician services events. Data for clinician services categories evaluated is available in the supplementary material.

Facility-related costs were reduced by − $2,718,819 per 1000 patients, per year, or − $2719 per patient versus controls, and clinician-related services were increased by − $72,833, or − $72.83 per patient. Total costs were − $2,791,652, or − $2791 per patient lower for the reSET-O cohort compared to controls.

Among those patients on buprenorphine therapy ($n = 619$ in the reSET-O cohort, $n = 650$ in the control cohort) the adjusted mean buprenorphine MPR was significantly greater in the reSET-O group at 0.848 (SE 0.0110)

Table 1 Demographics and clinical characteristics

Demographic/characteristic	Control cohort (N = 978)	reSET-O cohort (N = 901)	P value
Age (years), mean (SD)	39.2 (10.18)	37.9 (8.84)	0.004
Sex, n (%)			0.001
Female	539 (51.1%)	562 (62.4%)	
Male	439 (44.9%)	339 (37.6%)	
Payer, n (%)			0.001
Commercial	137 (14.0%)	96 (10.7%)	
Medicaid	640 (65.4%)	666 (73.9%)	
Medicaid advantage	25 (2.6%)	17 (1.9%)	
Unknown	176 (18.0%)	122 (13.5%)	
Census region, n (%)			< 0.001
Middle Atlantic	509 (52.0%)	370 (41.1%)	
East South Central	269 (27.5%)	341 (37.8%)	
East North Central	67 (6.9%)	81 (9.0%)	
West South Central	22 (2.4%)	50 (5.1%)	
South Atlantic	55 (5.6%)	62 (6.9%)	
Other	28 (2.9%)	25 (2.8%)	
Charlson comorbidity score			0.457
Mean (SD)	0.566 (1.2425)	0.609 (1.251)	
Mental health disorder, n (%)	492 (50.3%)	441 (48.9%)	0.556
Non-OUD substance use disorder, n (%)	578 (59.1%)	514 (57.0%)	0.368
Buprenorphine treatment			
Pre-index or post-index period (N)	716	665	
Post-index period, n (%)	637 (95.8%)	680 (95.8%)	0.133
Pre-index period, n (%)	686 (95.8%)	647 (97.3%)	0.470
Both pre-index and post-index periods, n (%)	650 (90.8%)	619 (93.1%)	0.118

SD standard deviation

(P < 0.001), compared to the control cohort of 0.761 (SE 0.0108) (P < 0.001).

Patients Covered by Medicaid

In analyses in the Medicaid subpopulation there were 666 patients treated with reSET-O (median age 36 years; 66.4% female, 33.2% from mid-Atlantic region, and 48.9% from east south central region, 94.5% treated with buprenorphine in both pre- and post-index periods), and 640 controls (median age 37 years; 59.2% female, 43.8% mid-Atlantic, and 39.5% east south central region, 92.8% treated with

Table 2 reSET-O comparative analysis of hospital facilities services over 12 months

Resource	Control cohort (N = 978)			reSET-O cohort (N = 901)					
	n (%)	Incidence	95% CI	n (%)	Incidence	95% CI	IRR	95% CI	p value
Unique hospital encounters	400 (40.9%)	0.899	(0.808, 1.000)	349 (38.7%)	0.791	(0.705, 0.886)	0.88	(0.75, 1.03)	0.105
Inpatient stays	141 (14.4%)	0.178	(0.148, 0.215)	97 (10.8%)	0.129	(0.104, 0.160)	0.72	(0.55, 0.96)	0.026
ICU stays	28 (2.9%)	0.035	(0.023, 0.053)	24 (2.7%)	0.024	(0.015, 0.040)	0.70	(0.38, 1.30)	0.258
Readmissions	31 (3.2%)	0.026	(0.016, 0.043)	10 (1.1%)	0.011	(0.006, 0.022)	0.44	(0.20, 0.93)	0.033
Partial hospitalizations	18 (1.8%)	0.093	(0.076, 0.115)	5 (0.6%)	0.028	(0.019, 0.042)	NA	NA	NA
ED visits—not admitted	353 (36.1%)	0.651	(0.582, 0.729)	308 (34.2%)	0.606	(0.538, 0.683)	0.93	(0.79, 1.09)	0.386
HOPD visits	25 (2.6%)	0.019	(0.012, 0.031)	17 (1.9%)	0.020	(0.012, 0.034)	1.06	(0.54, 2.05)	0.874

Incidence and IRR calculated from a negative binomial model of count of stays/visits adjusted for age, sex, region, payer type, Charlson comorbidity index score, and number of similar services in the 12 months prior to index date, with an offset for the number of days in the post-index period

CI confidence interval, ED emergency department, HOPD hospital outpatient department, IRR incidence rate ratio, NA not applicable

buprenorphine in both pre- and post-index periods). Pre-index MPR was similar in both cohorts (reSET-O: 0.632; controls: 0.624; $P = 0.622$).

Full data for patients with Medicaid coverage and differences in facility and clinician services between reSET-O users and controls are shown in the supplementary material. Briefly, there were 70 fewer ED visits, and 65 fewer inpatient stays per 1000 patients (which included 20 fewer ICU stays versus controls). In total, reSET-O-treated patients had 145 fewer unique hospital encounters over 12 months. Clinician services were increased by a total of 4363 events; the categories with the largest difference were E&M outpatient visits (2030 additional events), E&M: case management (1877 additional events), medicine: psychiatry (1028 additional events), pathology and laboratory: drug assay (827 fewer events), and E&M: hospital inpatient services (504 fewer events).

Cost comparisons in the Medicaid population revealed that facility-related costs were reduced by − \$4,008,370 per 1000 patients, per year, or − \$4008 per patient versus controls, and clinician-related services were increased by \$172,158, or \$172 per patient. Total costs were − \$3,832,284, or − \$3832 per patient lower for the reSET-O cohort compared to controls.

Among those patients on buprenorphine therapy ($n = 498$ in the reSET-O cohort, $n = 478$ in the control cohort) the adjusted mean buprenorphine MPR was significantly greater in the reSET-O group at 0.854 (SE 0.0120) ($P < 0.001$), compared to the control cohort of 0.762 (SE 0.0122) ($P < 0.0001$).

Adjustment for Baseline Mental Health and Substance Use Disorders

The analysis models were further adjusted for both mental health and substance use disorders by adding an indicator variable for each disorder. Both SUD and psychologic disorder were highly significant in the model for the majority of HCRU outcomes, with the presence of SUD or psychologic disorder being associated with a higher incidence of HCRU in the 12 months post index. As the distribution of SUD and mental health disorders was similar across the reSET-O and control cohorts (Table 1), the resulting IRRs comparing the cohorts were similar to those of the original model (Table 3). In general, baseline HCRU had the strongest association with post-index HCRU, followed by baseline SUD, age/region/payer, and baseline mental health disorders (data not shown).

Table 3 Comparison of model results

Mode type	IRRs: Model with adjustment for baseline patient characteristics			IRRs: Model with adjustment for baseline characteristics and concomitant baseline mental health and substance use disorders		
	IRR	95% CI	P value	IRR	95% CI	P value
Unique hospital encounters	0.88	(0.75, 1.03)	0.105	0.87	(0.74, 1.01)	0.072
Inpatient stays	0.72	(0.55, 0.96)	0.026	0.72	(0.55, 0.96)	0.023
ICU stays	0.70	(0.38, 1.30)	0.258	0.70	(0.38, 1.31)	0.264
Readmissions	0.44	(0.20, 0.93)	0.033	0.45	(0.21, 0.95)	0.037
Partial hospitalizations	NA	NA	NA	NA	NA	NA
ED visits	0.93	(0.79, 1.09)	0.386	0.92	(0.79, 1.08)	0.332
HOPD visits	1.06	(0.54, 2.05)	0.874	1.05	(0.50, 2.21)	0.903

NA not applicable. As a result of the small number of patients and/or visits, the binomial model could not be fit; thus, incidence is not calculated

DISCUSSION

In this 12-month follow-up study of patients with OUD, those treated with the reSET-O PDT had greater use of clinician services, experienced clinically meaningful increases in buprenorphine adherence, and incurred lower overall costs, which were driven by clinically meaningful decreases in unique hospital encounters, inpatient stays, hospital readmissions, ICU stays, and ED visits. These findings are consistent with previously published analyses of this PDT evaluating 6-month (pre-post) [25] and 9-month (vs. control) [20] HCRU outcomes, and provide evidence of clinically meaningful and statistically significant durability of effect [25].

Also, consistent with previous analyses [26], reductions in healthcare utilization and costs over the 12-month period were greater in the reSET-O cohort vs. controls (− $2791). A subgroup analysis of Medicaid patients vs. controls showed an even greater difference in favor of reSET-O treated patients (− $3832/patient over 12 months), which carries important financial implications for states as they disproportionately bear the burden of the OUD epidemic and its ever-increasing costs.

The observed increases in the use of outpatient, case management, and psychiatric, alcohol, and substance-related services in the pre/post and versus control analyses may indicate greater patient engagement with treatment. Similarly, the decreased use of pathology and laboratory-related and E&M hospital-related services observed in these analyses may indicate an improvement or stabilization of other conditions affecting these patients. Notably, clinically meaningful differences in hospital facility-related encounters were observed in all analyses. However, patients covered by Medicaid had the highest differences in facility-related encounters, specifically for inpatient services, ED and ICU stays, which helped drive the greater cost reductions observed. Supporting these observations are studies by Ruetsch and colleagues and Lynch and colleagues that have also shown decreased emergency department and inpatient visits in

patients with more comprehensive therapy [8] and with adherence to MOUD [7].

The significant increase in the rate of post-index buprenorphine adherence is noteworthy because of the similar MPR observed in both groups in the pre-index period, and because patients retained in MOUD are in a better position to avoid exposure to illicit opioids, and thus reduce their risk of overdose or an acute care event. Retention in treatment is essential to achieving long-term recovery, so interventions that improve retention should be prioritized.

The COVID-19 pandemic, it should be noted, was an important consideration in this analysis. To evaluate the potential impact of the COVID-19 pandemic, an adjustment was made for the number of days after March 11, 2020 within each patient's observation period. However, when this adjustment was made, no statistically significant effects on the results were observed, resulting in the COVID-19 adjustment being dropped from the model. This was expected since both arms in the comparative analyses were subject to a similar impact from the pandemic.

Over the past several years, substantial strides have been made to expand the use of MOUD. Despite this expansion, however, and the granting of flexible availability, such as via telemedicine prescribing and virtual visits, the prevalence of OUD and rate of overdoses have accelerated. MOUD expansion alone is thus insufficient. Additional treatment options that bring accessible, evidence-based treatments into standard care are essential.

Ironically, even though patients in recovery use far fewer costly hospital-related resources and hence cost the healthcare system far less than untreated patients, barriers to accessing treatment prevent many patients from obtaining the care and support they desperately need in order to achieve greater stability in their lives. PDTs, which can eliminate geographical, economic, stigma-related, and logistical barriers, may provide patients with broader access to interventions demonstrated to improve retention in treatment.

Strength and Limitations

Despite conducting a vs. control comparison to help alleviate concerns about regression to the mean, it is possible that latent differences may exist between the two groups (e.g., differences in buprenorphine dose at baseline and incidences of symptoms of depression or anxiety). However, the vs. control analysis also controlled for multiple covariates (age, sex, region payer type, CCI, mental health disorders, substance use disorders, and baseline HCRU) to help mitigate these concerns. Buprenorphine dose was not controlled for because dose was not available; however, no difference in the presence of buprenorphine prescriptions in the pre-index period was observed, and time on buprenorphine treatment was similar in both groups. It was not possible to assess the impact of race on HCRU outcomes because of the lack of such information in claims data.

Healthcare claims-based analyses have some inherent limitations, such as their administrative nature (i.e., built for adjudicating healthcare claims, not for research purposes), the possible presence of coding errors, lack of coding for all health conditions affecting patients, and lack of clinical or patient characteristics information (e.g., lab results, biomarkers, social determinants of health, disease severity). However, despite the well-known limitations related to claims data analyses, the real-world data presented in this study have greater external generalizability and validity than data derived from clinical trials by virtue of their inclusion of diverse populations using the product without external guidance or incentives for participation or attendance at follow-up visits from investigators. This study did not exclude patients on the basis of comorbid conditions, and evaluated all HCRU incurred by patients over the observation period, making it a rigorous evaluation of the long-term performance of reSET-O in this difficult-to-treat patient population.

CONCLUSIONS

In an evaluation of a diverse, real-world, all-comer population of patients with OUD, significantly fewer unique hospital encounters, inpatient stays, and ED visits were observed 12 months after treatment initiation with reSET-O compared to patients who did not initiate reSET-O. Use of reSET-O was associated with per-patient cost reductions, which were greater in the Medicaid subpopulation.

ACKNOWLEDGEMENTS

Analytics, which participated in this study under contract with Pear Therapeutics (US), Inc. Sean Murphy is not an employee of Pear Therapeutics, Inc., and was not compensated to perform the research for his role as an author.

Compliance with Ethics Guidelines. This study received a waiver of authorization for the use and disclosure of protected health information (PHI) and a determination of exempt status under 45 CFR § 46.104(d)(4) from Western Institutional Review Board on October 21, 2021.

Data Availability. The datasets generated during and/or analyzed during the current study are not publicly available because the data source (Health Verity) requires licensees (i.e., Pear Therapeutics (US), Inc.) to purchase data directly from them.

Open Access. This article is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License, which permits any non-commercial use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by-nc/4.0/.

REFERENCES

1. Centers for Disease Control & Prevention. Understanding the epidemic 2019. https://www.cdc.gov/drugoverdose/epidemic/index.html. Accessed 29 Mar 2022.

2. Ciccarone D. The rise of illicit fentanyls, stimulants and the fourth wave of the opioid overdose crisis. Curr Opin Psychiatry. 2021;34(4):344–50.

3. Centers for Disease Control & Prevention. Increse in fatal drug overdoses across the United States driven by synthetic opioids before and during the COVID-19 pandemic. https://emergency.cdc.gov/han/2020/han00438.asp?ACSTrackingID=USCDC_511-DM44961&ACSTrackingLabel=HAN%20438%20-%20General%20Public&deliveryName=USCDC_511-DM44961. Accessed 29 Mar 2022.

4. Centers for Disease Control & Prevention. Vital statistics rapid release: provisional drug overdose death counts. https://www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm. Accessed 29 Mar 2022.

5. Centers for Disease Control & Prevention. Nonfatal drug overdoses. https://www.cdc.gov/drugoverdose/nonfatal/index.html. Accessed 29 Mar 2022.

6. Assistant Secretary for Planning and Evaluation, US Department of Health and Human Services. Nonfatal opioid overdose and associated health outcomes: final summary report September 2019. https://aspe.hhs.gov/reports/non-fatal-opioid-overdose-associated-health-outcomes-final-summary-report-0. Accessed 29 Mar 2022.

7. Ruetsch C, Tkacz J, Nadipelli VR, et al. Heterogeneity of nonadherent buprenorphine patients: subgroup characteristics and outcomes. Am J Manag Care. 2017;23(6):e172–9.

8. Lynch FL, McCarty D, Mertens J, et al. Costs of care for persons with opioid dependence in commercial integrated health systems. Addict Sci Clin Pract. 2014;9(1):16.

9. Ronquest NA, Willson TM, Montejano LB, Nadipelli VR, Wollschlaeger BA. Relationship between buprenorphine adherence and relapse, health care utilization and costs in privately and publicly insured patients with opioid use disorder. Subst Abuse Rehabil. 2018;9:59–78.

10. American Society of Addiction Medicine. National practice guideline for the treatment of opioid use disorder, 2020 Focused Update.

11. Substance Abuse and Mental Health Services Administration. TIP 63: medications for opioid use disorder (updated 2021). https://store.samhsa.gov/sites/default/files/SAMHSA_Digital_Download/PEP21-02-01-002.pdf. Accessed 29 Mar 2022.

12. Christensen DR, Landes RD, Jackson L, et al. Adding an internet-delivered treatment to an efficacious treatment package for opioid dependence. J Consult Clin Psychol. 2014;82(6):964–72.

13. Velez FF, Colman S, Kauffman L, Ruetsch C, Anastassopoulos K. Real-world reduction in healthcare resource utilization following treatment of opioid use disorder with reSET-O, a novel prescription digital therapeutic. Expert Rev Pharmacoecon Outcomes Res. 2021;21(1):69–76.

14. Moore BA, Fiellin DA, Cutter CJ, et al. Cognitive behavioral therapy improves treatment outcomes for prescription opioid users in primary care buprenorphine treatment. J Subst Abuse Treat. 2016;71:54–7.

15. National Institute on Drug Abuse. Principles of drug addiction treatment: a research-based guide (third edition): drug addiction treatment in the United States. https://www.drugabuse.gov/publications/principles-drug-addiction-treatment-research-based-guide-third-edition/drug-addiction-treatment-in-united-states. Accessed 29 Mar 2022.

16. Pear Therapeutics Inc. reSET-O [clinician directions for use]. 2017.

17. Campbell AN, Nunes EV, Matthews AG, et al. Internet-delivered treatment for substance abuse: a multisite randomized controlled trial. Am J Psychiatry. 2014;171(6):683–90.

18. Maricich YA, Bickel WK, Marsch LA, Gatchalian K, Botbyl J, Luderer HF. Safety and efficacy of a prescription digital therapeutic as an adjunct to buprenorphine for treatment of opioid use disorder. Curr Med Res Opin. 2021;37(2):167–73.

19. Maricich YA, Gerwien R, Kuo A, Malone DC, Velez FF. Real-world use and clinical outcomes after 24 weeks of treatment with a prescription digital therapeutic for opioid use disorder. Hosp Pract. 2021;2:1–8.

20. Velez F, Colman S, Kauffman L, et al. Comparison of healthcare resource utilization between patients who engaged or did not engage with a prescription digital therapeutic for opioid use disorder. ClinicoEconomics Outcomes Res. 2021;13:909–16.

21. Cramer JA, Roy A, Burrell A, et al. Medication compliance and persistence: terminology and definitions. Value Health. 2008;11(1):44–7.

22. Arifkhanova A, McCormick Kraus E, et al. Estimating costs of hospitalizations associated with opioid use disorder or opioid misuse at a large, urban safety-net hospital-Denver, Colorado, 2017. Drug Alcohol Depend. 2021;218: 108306.

23. Centers for Medicare and Medicaid Services (CMS). Medicare Hospital Outpatient Prospective Payment System Addendum A, April 2020 file. 2020. https://www.cms.gov/Medicare/Medicare-Fee-For-Service-Payment/HospitalOutpatientPPS/Addendum-A-and-Addendum-B-Updates. Accessed 29 Mar 2022.

24. Peterson C, Li M, Xu L, Mikosz CA, Luo F. Assessment of annual cost of substance use disorder in US hospitals. JAMA Netw Open. 2021;4(3): e210242.

25. Velez FF, Colman S, Kauffman L, Anastassopoulos K, Murphy S, Maricich Y. Real-world changes in US health system hospital-based services following treatment with a prescription digital therapeutic for opioid use disorder. Hosp Pract. 1995;2021:1–7.

26. Velez FF, Ruetsch C, Maricich Y. Evidence of long-term real-world reduction in healthcare resource utilization following treatment of opioid use disorder with reSET-O, a novel prescription digital therapeutic. Expert Rev Pharmacoecon Outcomes Res. 2021;21(4):519–20.