Routledge
Taylor & Francis Group

Cost-Effectiveness Analysis of a Prescription Digital Therapeutic for the Treatment of Opioid Use Disorder

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ABSTRACT

The lack of adequate treatment for many patients with opioid use disorder (OUD) has led to high medical costs ($90B in 2020). An analysis of the cost-effectiveness (cost-utility) of reSET-O, the first and only FDA-approved prescription digital therapeutic (PDT) for the treatment of OUD, is needed to inform value assessments and healthcare decision making. To evaluate the cost-utility of reSET-O in conjunction with treatment-as usual (TAU) compared to TAU alone. A third-party payer-perspective decision analytic model evaluated the cost-effectiveness of reSET-O + TAU relative to TAU (i.e., oral buprenorphine, face-to-face counseling, and contingency management [immediate rewards for negative drug tests logged]) alone over 12 weeks. Clinical effectiveness data (retention in therapy and health state utilities) were obtained from the peer-reviewed literature, while resource utilization and cost data were obtained from a published claims data analyses. Over 12 weeks, the addition of reSET-O to TAU resulted in a gain of 0.003 quality-adjusted life years (QALYs), and $1,014 lower costs, resulting in economic dominance vs. TAU. reSET-O + TAU's was economically dominant (less costly, more effective) vs. TAU alone over 12 weeks, a result that was driven by a reduction in medical costs after initiation of reSET-O observed in a recent real-world claims analysis.

Introduction

Opioid use disorder (OUD) is a chronic disease characterized by a cluster of cognitive, behavioral, and physiological symptoms indicating that an individual continues using opioid substances despite significant substance-related problems[1]. In the USA (US), since the 1990s, the incidence of OUD and overdose deaths involving opioids has reached epidemic proportions[2]. In 2019, an estimated 9.7 million individuals in the US misused opioids and 1.6 million individuals in the US had an OUD [3]. The current COVID-19 epidemic is compounding the opioid epidemic with increased isolation, risk of depression and increased barriers to care due to social distancing measures. Many states have reported an increase in overdoses since the start of the pandemic[4].

Despite the increasing use of opioids and the increase in opioid-related deaths in the US, most individuals do not receive OUD treatment[5]. Pharmacotherapy (i.e., buprenorphine, methadone, or naltrexone) combined with counseling and behavioral therapy is the recommended first-line treatment for OUD, and is known as medication-assisted therapy (MAT) [6,7]. Medications work to reduce cravings for illicit opioids and/or reduce withdrawal symptoms, while neurobehavioral therapy is needed to support long-term substance avoidance skills and to help restore patients' enjoyment of healthy interpersonal, social, and vocational activities that have been displaced by substance use.

Retention in therapy is an outcome of paramount importance in the treatment of opioid use disorders, with research indicating that most individuals need at least 3 months in treatment to significantly reduce or stop their drug use and that the best outcomes occur with longer durations of treatment [6,8–14]. Barriers preventing broader access to OUD treatment include stigma, inadequate professional education and training related to the evidence base for using medication, and challenges in connecting individuals with appropriate OUD treatment (time, distance and financial challenges), and also work against patients being retained in treatment over the long term [15,16]. The lack of adequate treatment for many OUD patients has led to high medical costs associated with OUD (projected at $90B in 2020, equivalent to more than $40,000 per patient per year [17]). OUD is responsible for approximately 585,000 emergency department (ED) visits each year, nearly half of which result in inpatient

admissions, and the 30-day readmission rate for patients hospitalized with OUD is 24%[18].

Even when patients have access to treatment, dropout rates are high (30% over one month and 50% or higher at three months and beyond) [19–23]. This is why healthcare strategies to improve access and adherence to OUD treatment are of paramount importance to patients and payers.

reSET-O® is the first and only prescription digital therapeutic (PDT) currently authorized by the FDA for the treatment of OUD. The FDA authorization of reSET-O was based on a randomized-controlled trial (RCT) of its academic precursor, the Therapeutic Education System (TES)[24]. The reSET-O therapeutic delivers treatment based on the community reinforcement approach (CRA), an intensive form of cognitive behavioral therapy (CBT) indicated as part of the gold standard treatment for OUD, along with other neurobehavioral therapies such as fluency training (to reinforce learning), and contingency management (to reward positive behaviors)[25]. reSET-O, in conjunction with treatment as usual (TAU; i.e., oral buprenorphine, face-to-face counseling, and contingency management [CM; immediate rewards for negative drug tests logged]), showed significantly increased retention in OUD treatment vs. TAU alone over 12 weeks (80.4% vs 64.1%, respectively)[24], and was ultimately FDA-authorized for this indication in 2018. An analysis of the likelihood of abstinence from opioids and cocaine in this study population showed reSET-O-treated patients were also more likely to be abstinent during weeks 9–12, the final month of treatment (reSET-O+ TAU: 75.9% abstinent, vs. TAU: 60.6%; OR: 2.08; 95% CI 1.10–3.95; P = 0.0248) [26–29].

The economic value of reSET-O has been increasingly studied. An analysis of the cost-utility of reSET-O from the perspective of increased retention in OUD treatment is needed to inform whether reSET-O will provide value beyond TAU, and at what cost. Therefore, the objective of this study was to evaluate the clinical and economic impact of reSET-O in conjunction with TAU compared to TAU alone based on treatment retention data from the pivotal RCT that supported reSET-O's FDA authorization.

Methods

Study design and model structure

A decision analytic model evaluated the cost-effectiveness of reSET-O in conjunction with TAU (reSET-O + TAU) relative to TAU alone. The model's perspective is that of the third-party payer, and the time horizon of the model was 12 weeks (the duration of one prescription for reSET-O). Patients treated with reSET-O + TAU or TAU alone were considered not retained in therapy based on their voluntary departure from the trial or after missing three consecutive visits as defined in the pivotal clinical trial by Christensen, et al. (Figure 1).

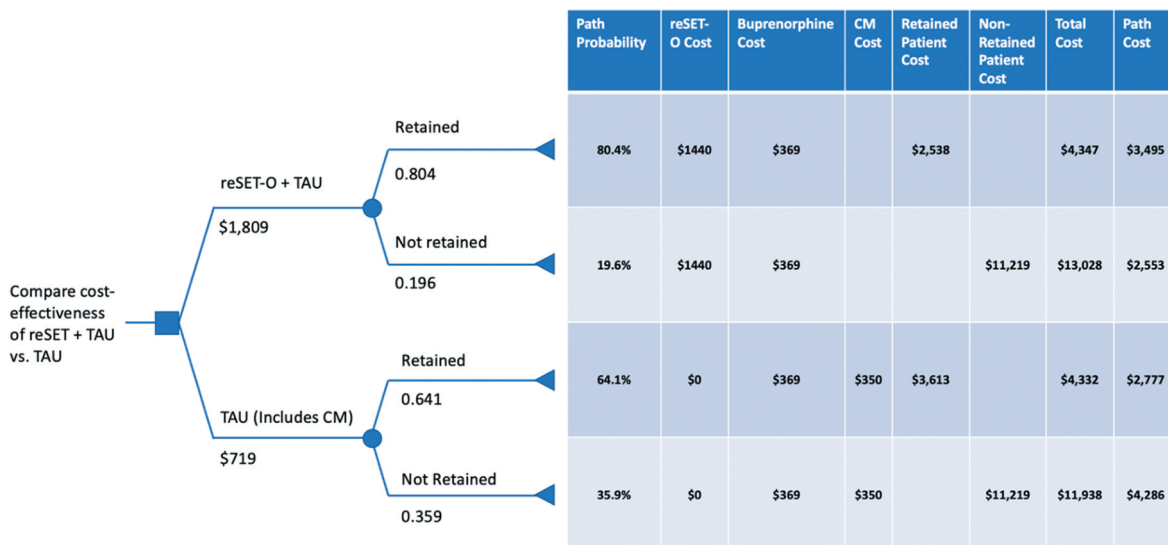| Path Probability	reSET-O Cost	Buprenorphine Cost	CM Cost	Retained Patient Cost	Non-Retained Patient Cost	Total Cost	Path Cost
80.4%	$1440	$369		$2,538		$4,347	$3,495
19.6%	$1440	$369			$11,219	$13,028	$2,553
64.1%	$0	$369	$350	$3,613		$4,332	$2,777
35.9%	$0	$369	$350		$11,219	$11,938	$4,286

Figure 1. Decision analytic model evaluating the cost-effectiveness of reSET-O with TAU (reSET-O + TAU) vs. TAU (i.e., oral buprenorphine, face-to-face counseling, and CM) alone CM, contingency management; OUD, opioid use disorder; TAU, treatment-as-usual.

Note: TAU includes oral buprenorphine, face-to-face counseling, and contingency management (CM).

Decision analytic model inputs

Clinical inputs

Retention rates (reSET-O+ TAU: 80.4%; vs. TAU: 64.1%) were obtained from Christensen et al. (2014) (Table 1) [24]. Health state utilities were obtained for retained and non-retained patients from Wittenberg et al., 2017[26] (0.761 for retained patients [similar to patients on stable buprenorphine therapy] vs. 0.694 for non-retained patients [similar to patients with active opioid use]) (Table 1).

Economic inputs

The cost of a 12-week prescription of reSET-O was assumed to be $1,440 based on the Red Book wholesale acquisition cost (WAC) cost of $1,665 and assuming a discount of 13.5%. CM implementation and administration costs of $350 were only included for TAU alone as they are already included in the reSET-O cost. TAU costs over 12 weeks were obtained from an analysis of an early real-world (all-comer) cohort of reSET-O-treated patients (mean age 37 years, 60% female, 82.6% Medicaid) which evaluated total facility and medical services utilization in the 6 months prior to reSET-O initiation (cost input for TAU: $3,613) vs. the 6-months after reSET-O initiation (cost input for reSET-O+ TAU: $2,538)[30]. Costs of non-retained patients ($11,219 over 12 weeks) was obtained from a recent analysis by Wang et al., 2017[31,32]. Buprenorphine costs were $369 over 12 weeks (3 prescriptions at $123/prescription) (Table 1).

Analyses

Clinical and economic results (consequences) were presented in a simple, disaggregated form to provide decision makers with as broad a view as possible of the consequences of the two interventions. Clinical effectiveness was presented as the number of quality-adjusted life years (QALYs) for each treatment arm over 12 weeks. Disaggregated costs for the two treatment arms included the cost of reSET-O, CM costs, treatment intervention costs (i.e., facility and medical services costs), buprenorphine costs, and medical costs associated non-retention in treatment. One-way sensitivity analyses were performed by varying inputs by 5% to assess impact on cost outcomes.

Results

Base case

Over 12 weeks, the impact on costs and QALYs with reSET-O+ TAU vs. TAU was -$1,014 and 0.003, (Table 2).

Sensitivity analysis

One-way sensitivity analysis showed that a 5% variation of cost and health utility inputs resulted in reSET-O being dominant in all cases; varying the cost of non-retained patients resulted in the largest variation in output although both high and low inputs resulted in reSET-O being economically dominant (low: -$78,615.80/QALY; high: -$94,199.13/QALY). Utility inputs for retained and not retained patients produced the largest overall changes in cost reductions per QALY gained (Table 3).

Table 1. Clinical and economic model inputs for reSET-O+ TAU vs. TAU cost-effectiveness model.

	reSET-O + TAU	TAU	Source
Clinical Inputs			
% Likelihood Abstinent	80.4%	64.1%	Christensen et al., 2014[24]
Standard Gamble Health Utilities			
Retained	0.766		Wittenberg et al., 2016[26]
Not retained	0.694		
Economic Inputs			
reSET-O	$1,440/ prescription	$0	Red Book, assumes 13.5% discount off $1,665 WAC
Contingency Management (CM)	Included with reSET-O	$350/12 weeks	Sindelar et al., 2007[28]; Petry et al., 2014[29] adjusted to 2020 US$
Buprenorphine	$369/12 weeks	$369/12 weeks	Red Book
Treatment-As-Usual (TAU) (for retained patients)			
Facility Costs (IP, ICU, ED, Partial hospitalizations and Observation visits)	$1,568/12 weeks	$708/12 weeks	Velez et al., 2020[30]
Medical Services Costs (laboratory, E&M, and medical services)	$2,045/12 weeks	$1,830/ 12 weeks	
Total	$2,538/12 weeks	$3,613/ 12 weeks	
Costs of non-retained patients	$11,219/12 weeks		Wang et al., 2020[31]

CM, contingency management; CMS, Centers for Medicare and Medicaid Services; SF, Short-Form; TAU, treatment-as-usual; WAC, wholesale acquisition cost.

Table 2. Base case clinical and economic consequences and cost-effectiveness of reSET-O + TAU vs. TAU.

	reSET-O + TAU	TAU	Incremental Difference
Clinical Consequences			
% of patients abstinent	75.9%	60.6%	15.3%
QALYs	0.75188	0.74015	0.00271
Economic Consequences			
reSET-O	$1,440	$0	$1,440
CM cost	$0	$350	-$350
Cost of buprenorphine	$369	$369	$0
Medical costs for retained patients	$2,041	$2,316	-$275
Medical costs for non-retained patients	$2,199	$4,028	-$1,829
Total Costs	***$6,049***	***$7,063***	***-$1,014***
Cost-effectiveness			***economically dominant***

CM, contingency management; QALY, quality-adjusted life year; TAU, treatment-as-usual.

Table 3. Sensitivity analysis of 5% variation in model inputs.

	Cost/QALY Low	Cost/QALY High	Cost-effectiveness
reSET-O Cost	-$92,542.43	-$80,272.49	
Buprenorphine cost	-$86,407.46	-$86,407.46	
Cost of CM	-$84,916.33	-$87,898.60	***economically dominant (less costly, more effective)***
Costs not retained	-$78,615.80	-$94,199.13	
Utilities Retained	-$182,980.51	-$41,753.94	
Utilities Not Retained	-$44,122.96	-$2,073,779.14	

Discussion

This analysis found reSET-O + TAU was shown to be economically dominant (i.e., 0.0027 QALYs more effective and $1,014 less costly) compared to TAU alone over 12 weeks. Reductions in medical costs after initiation of reSET-O exceeded the amount needed to offset the cost of the PDT, while greater retention in treatment drove QALY gains. One-way deterministic sensitivity analyses showed the model results to be robust, and reSET-O was economically dominant in all cases. Variation of health utility scores for retained and non-retained patients had the biggest impact on the results of the model although reSET-O remained economically dominant given its cost-reducing effect.

The challenge to healthcare payers and providers is to maximize the net benefits obtained from healthcare expenditures. Comparative effectiveness research intends to help identify cost-effective medical treatments and, in turn, help curb spending for expensive illnesses such as OUD. This change in spending trajectory is to be achieved, in part, through the selection of therapies that have been proven effective while providing value for investments.

Pharmacotherapy alone is rarely sufficient treatment for substance use disorders[33]. TAU in this modeling evaluation included face-to-face counseling (6 visits over 12 weeks) and CM, which may be challenging for many practices to implement due to limitations in available time, resources, and personnel. There is a significant gap of limited time and resources to provide adequate evidence-based neurobehavioral and pharmacological care to all patients in need of recovery treatment [34,35].

The addition of reSET-O to TAU increases the proportion of patients who are retained in therapy and ultimately results in improved quality of life and a gain of QALYs. These findings are consistent with prior studies which have shown an association between better patient OUD treatment retention and improved clinical and humanistic patient outcomes [36–38]. The burden associated with diminished quality of life from OUD extends beyond the individual, affecting the physical and mental health of the individual's family; however these QALY benefits were not captured in this analysis.

Relapse from OUD may lead to the transmission of infectious disease, criminal activity, or death[39]. As such, the ultimate treatment goal of patients with OUD is sustained abstinence and recovery of their lives[40]. Treatment is critical for achieving this goal as research has shown that individuals who begin and remain in treatment stop using opioids, decrease their criminal activity, and improve their occupational, social, and psychological functioning[40]. However, less than 35% of adults with OUD in 2019 received treatment for opioid use in the past year, highlighting the need for expanded access to comprehensive OUD treatment[41].

The limitations of this study are mostly those inherent to all decision analytic modeling studies. Economic models combine data from many different sources to inform decisions about resource allocation. They provide more explicit details regarding the potential implications of alternate decisions and therefore can be a valuable input for the decision-making process. However, the model represents a simplification of the complex factors involved in the clinical and economic outcomes of patients with OUD. Although every effort has been made to identify the most relevant inputs for inclusion in this model, the results may not be generalizable to all populations of patients with OUD, or to all regions, and should therefore be interpreted with care.

The utilization of a 12-week time horizon in this modeling evaluation may also be regarded as a limitation as OUD often requires long-term management. However, this use of a shorter time horizon is likely a conservative approach for estimating cost-

effectiveness as the benefits of reSET-O, reflected in new learned behaviors, drug refusal skills, and coping mechanisms, can be expected to continue to accrue long after treatment, as has been observed with other PDTs [42,43], with no additional cost incurred due to the device. Hence, the incremental cost-effectiveness would become more favorable. The 12-week time horizon has also been studied in two other published health economic evaluations of reSET-O; the first (Wang et al., 2020) [31] evaluated the impact of adherence with reSET-O but did not include impact on health utilities and therefore could not calculate a cost/QALY outcome, while the second (Velez, et al., 2021) [44] measured health utilities and calculated a cost/QALY based on abstinence rates from the pivotal clinical trial for reSET-O. Future studies should include economic analyses and real-world evidence of the impact of reSET-O beyond 12 weeks, and beyond third-party payers, as it is likely that other public costs related to criminal activity and lost productivity also would be impacted by increasing treatment adherence through PDTs[45].

Lastly, it should be noted that the TAU comparator in this analysis represents a level of care which was implemented in a clinical trial and which is seldom available to patients in usual-care settings. As a result, there is the potential for even greater QALY gains with reSET-O vs TAU, which should also be evaluated in future studies.

Conclusion

reSET-O + TAU's economic dominance (reduced costs, greater effectiveness) vs. TAU alone over 12 weeks was driven by a reduction in medical costs observed in a real-world claims analysis of reSET-O-treated patients.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

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