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Safety and efficacy of a prescription digital therapeutic as an adjunct to buprenorphine for treatment of opioid use disorder

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ABSTRACT

Objectives: To evaluate the safety and efficacy of a digital therapeutic in treatment-seeking individuals with opioid use disorder (OUD) in an analysis of randomized clinical trial (RCT) data (ClinicalTrials.gov identifier: NCT00929253).

Methods: Secondary analysis of an RCT including 170 adults meeting DSM-IV criteria for OUD. Participants were randomized to 12-weeks of treatment-as-usual (TAU) or TAU plus a digital therapeutic providing 67 digital, interactive educational modules based on the Community Reinforcement Approach. TAU consisted of buprenorphine maintenance therapy, 30 min biweekly clinician interaction, and abstinence-based contingency management. Primary endpoints were treatment retention and abstinence (negative urine drug screen) during weeks 9–12 of treatment. Safety was assessed by evaluating adverse events.

Results: Participants randomized to TAU plus a digital therapeutic had significantly greater odds of opioid abstinence during weeks 9–12 compared to TAU: 77.3 versus 62.1%, respectively (p=.02), OR 2.08, 95% CI 1.10–3.95. The risk of patients leaving treatment was significantly lower in the digital therapeutic group (HR 0.49, 95% CI 0.26–0.92). No significant difference was observed in the rate of adverse events between groups (p=.42).

Conclusions: A prescription digital therapeutic (PDT) in combination with buprenorphine therapy improves clinically significant patient outcomes including abstinence from illicit opioids and retention in treatment compared with treatment as usual.

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Introduction

In 2019, almost 2 million adults aged 18 and older in the United States (US) had an opioid use disorder (OUD)[1]. Fatal opioid overdoses have skyrocketed over the past decade, killing 51,574 people in the 12-month period ending February, 2020[2]. The opioid epidemic in the US and globally has highlighted the need for much wider access to pharmacological and behavioral treatments for OUD.

Medications for opioid use disorder (MOUD) along with behavioral therapy, are standard of care for OUD[3]. Despite the availability of MOUD, 80–90% of individuals who need treatment do not receive care[4]. Common reasons for this trend include refusal to seek treatment, high cost of care, stigma, and lack of or limited access to treatment[5]. These difficulties are magnified in rural communities, where substance use treatment centers and providers can be difficult to physically reach.

Evidence-based behavioral approaches for OUD are resource-intensive and challenging to implement as they require intensive training and ongoing supervision to ensure correct and consistent delivery[6,7].

A computer-based therapeutic was developed to deliver behavioral therapy based on the Community Reinforcement Approach (CRA). CRA is an evidence-based behavioral therapy designed for patients with substance use disorders[8]. CRA reinforces abstinence from drug use by encouraging behaviors that improve employment status, family and social relations, and increased recreational activities[9]. The therapeutic (academic name Therapeutic Education System [TES][10]) was evaluated in two RCTs that formed the evidence base on which FDA authorization of the reSET-O PDT was based[11,12]. TES, delivered via a web browser, used clinical content and a mechanism of action equivalent to reSET-O, which delivers prescribed content via mobile devices (i.e. smart phones and tablets).

The digital therapeutic treats patients with OUD by combining CRA therapy with fluency training (to reinforce concept mastery), and contingency management (CM), an evidence-based form of motivational incentives[13]. The combination of CRA and CM has been shown to improve substance use treatment outcomes when delivered either by a clinician or digitally[10–12,14,15].

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The efficacy of the digital therapeutic was evaluated in a 2014 RCT of 170 adults with OUD at the Center for Addiction Research, University of Arkansas for Medical Sciences[12]. This study did not report safety outcomes, however. It also did not evaluate abstinence from individual substances, and it did not characterize abstinence during the last four weeks of the 12-week study treatment period, which is the current approach recommended by the National Institute of Drug Abuse[16]. The objective of this study was to further evaluate the efficacy of the digital therapeutic in treatment-seeking individuals with OUD by analyzing abstinence data in the last four weeks of treatment for both cocaine use and opioid use in order to ascertain any unique impacts of treatment with TES on these specialized populations of patients with substance use disorders (SUDs). Safety data, which have not been reported previously, were analyzed to evaluate any associations between use of a digital therapeutic and adverse events typical of patients with OUD.

Methods

Participants and setting

The design and conduct of this RCT have been described previously[12]. A total of 206 individuals were consented and assessed for eligibility. After exclusion of 36 individuals for lack of intake assessments or other reasons, 170 individuals with OUD were enrolled in the study. All participants provided written informed consent. Participants were at least 18 years old, in good health, met DSM-IV criteria for opioid dependence, qualified for buprenorphine treatment, had no active psychiatric disorder, no unstable or significant medical illness, were not pregnant, and were not incarcerated. The study was registered as NCT00929253 on ClinicalTrials.gov, approved by University of Arkansas Medical Sciences Investigator Review Board, and conducted according to Good Clinical Practices.

Randomization

All participants were inducted onto buprenorphine (sublingual mono tablet) using procedures described previously[12]. Following induction, randomization to either TAU or TAU plus the digital therapeutic was 1:1 and stratified based on buprenorphine stabilization dose, distance from the clinic, prior treatment status, and past month cocaine use. A designated study coordinator remained blind to the randomization schema until each participant's assignment was unlocked for implementation.

Treatment-as-usual (TAU)

Participants randomized to TAU received buprenorphine/naloxone and an every-other-week 30-minute meeting with a clinician. During the 30-minute clinician interaction, the patient reviewed his or her treatment progress. Participants provided urine samples in-clinic three times per week: Monday, Wednesday, and Friday. Urine specimens were tested for methadone, opioids, propoxyphene, cocaine, and once per week for benzodiazepines. Oxycontin testing was performed using a single-panel Oxycontin dipstick for a qualitative result. All participants were eligible for CM vouchers based on urine drug screen (UDS) results.

TAU plus digital therapeutic

The program used in the original study consisted of 67 interactive digital modules based on CRA, plus a user guide. Core modules focus on building basic cognitive- behavioral and relapse prevention skills and provide education on preventing infections (i.e. human immunodeficiency virus, hepatitis C virus, and other infections transmitted sexually or via shared needles). Supplemental modules target improvement of psychosocial functioning (e.g. managing relationships, building communication skills, employment status, time management, insomnia), in-depth training on preventing infections, and support for living with infections. Module completion was self-guided with no direct clinician supervision. Participants were asked to complete modules three times per week during weeks without a clinician visit, and twice per week during weeks with a clinician visit. Participants were able to revisit previously completed modules or complete a new module. In this clinical trial patients accessed the web-based therapeutic using in-clinic computers, whereas reSET-O delivers equivalent, prescribed clinical content via an application (app) downloaded to mobile devices (i.e. smartphones, tablets) from an app store with a prescription.

Medication

All participants received buprenorphine pharmacotherapy. Buprenorphine mono tablet was used for induction and buprenorphine/naloxone combination sublingual tablet (4:1 ratio) was used for maintenance and detoxification[12].

During the maintenance phase, participants were administered buprenorphine under observation at each clinic visit. Participants were provided a double-dose of buprenorphine on Mondays and Wednesdays and a triple-dose on Fridays. This dosing schedule is safe and effective, without causing intoxication or clinically significant withdrawal, and is supported by clinical guidelines[17,18]. At study completion, participants were either detoxified under supervision of the study physician or referred for continued treatment.

Contingency management (CM)

All participants were eligible for voucher incentives based on abstinence from opioids and cocaine determined via UDS. Vouchers were provided on an escalating scale, where the initial negative UDS was worth 10 points at $0.25 per point. For each subsequent negative UDS, the voucher value was increased by five points, and three consecutively negative UDS resulted in a $10 bonus. In the event of a positive UDS, the voucher value was reduced to the initial value, however after three consecutive negative UDS results the voucher value was increased to the level achieved before it was reduced. Participants could earn up to $997.50 for 12-weeks continuous abstinence.

Table 1. Participant demographic information.

Variable	TAU ($n = 79$)[a]	TAU + digital therapeutic ($n = 91$)	Total ($n = 170$)	p Value
Age (years)				
Mean (SD)	33.6 (9.80)	32.2 (9.85)	32.9 (9.82)	.34
Median	31	29	30	
Min	19	19	19	
Max	63	58	63	
Sex				
Male	47 (59.5%)	45 (49.5%)	92 (54.1%)	.22
Female	32 (40.5%)	46 (50.5%)	78 (45.9%)	
Race				
White	75 (94.9%)	87 (95.6%)	162 (95.3%)	.32
Black or African American	4 (5.1%)	2 (2.2%)	6 (3.5%)	
Other	0	2 (2.2%)	2 (1.2%)	
Other substance dependence				
Alcohol	43 (54.4%)	50 (54.9%)	93 (54.7%)	>.99
Cocaine	17 (21.5%)	14 (15.4%)	31 (18.2%)	.33
Benzodiazepines	47 (59.5%)	56 (61.5%)	103 (60.6%)	.88
Methamphetamine	10 (12.7%)	6 (6.6%)	16 (9.4%)	.20
Other drug	57 (72.2%)	67 (73.6%)	124 (72.9%)	.86

Data are mean (SD) or n (%).
[a]Seventy-nine participants were found to be randomized to receive TAU and 91 participants to receive TAU + digital therapeutic in the present analysis, whereas 78 participants were reported previously to receive TAU and 92 to receive TAU + digital therapeutic.

Outcomes

The primary study endpoints were abstinence and retention in treatment. Abstinence was assessed by UDS throughout the study. The primary endpoint evaluated abstinence during the last four weeks of treatment (weeks 9–12). Each UDS assessment was used to determine a participant's abstinence from opioids, cocaine or both, three times weekly. Total abstinence was defined as abstinence from both opioids and cocaine[12]. Participants were considered non-abstinent (i.e. positive) if the UDS indicated cocaine or opioid use for a given third-week time point, or if the sample was missing/not provided, which is a standard, and conservative, approach in the field of addiction research[16].

Retention in treatment was based on the number of days in treatment for each study participant. Dropout was defined as the time of the last face-to-face contact.

A secondary endpoint was the total number of one-third weeks abstinent (opioids and cocaine) for each participant over the 12-week study duration. Exploratory endpoints included likelihood of abstinence from opioids during the last 6–8 weeks of treatment.

Adverse events relevant to patients diagnosed with OUD (e.g. psychiatric events, gastrointestinal problems) were monitored from time of consent throughout the study. Adverse events were retrospectively coded to system organ classification using preferred terms of the Medical Dictionary for Regulatory Activities based on de-identified participant study records.

Statistical analysis

Baseline and demographic characteristics were described using means, standard deviations, and frequencies for the study sample. *T*-tests and chi-squared tests were used to evaluate differences between treatment groups for continuous and categorical variables, respectively.

The primary endpoint evaluated abstinence during the last four weeks of treatment (weeks 9–12) using a repeated measures logistic generalized estimating equations model with factors for treatment, time, and treatment × time[19,20]. Three categories of abstinence were evaluated: abstinence from opioids and cocaine, from opioids alone, and from cocaine alone. Dropout was considered an event and time to withdrawal from treatment was treated as time-to-event data. Values ranged from 0 to 81 days, with a maximum of 81 days for participants completing all 12 weeks of treatment. Retention rate was estimated at weeks 2, 4, 6, 8, 10, and 12, using the Kaplan-Meier method. Retention distribution between the two groups was compared using a log-rank test.

Difference in total one-third weeks abstinent was analyzed by two-sample *t*-test comparing group means. Descriptive statistics were used to summarize the number of modules completed by the TAU plus digital therapeutic group (mean, standard deviation, range).

Safety was evaluated using Fisher's exact test for comparison of adverse events.

Statistical analyses were conducted by a study-independent statistician and performed in SAS, version 9.3 or higher (SAS Institute). No adjustments for multiple comparisons were made. The sample size determination for this study has been described[12].

Results

Participant demographics

No significant differences were detected between treatment groups on any demographic variable (Table 1). Most participants were male (54.1%) and white (95.3%), with a mean age of 32.9 years. DSM-IV criteria for cocaine dependency was met in 21.5% of the TAU group and 15.4% of the TAU plus digital therapeutic group (difference not statistically significant).

Abstinence and retention

As shown in Table 2, participants randomized to TAU plus the digital therapeutic had a significant, increased likelihood of abstinence from opioids and cocaine during the last four

Table 2. Abstinence from substance use.

Variable	TAU ($n = 79$)	TAU + digital therapeutic ($n = 91$)	Odds ratio (95% CI)	p Value
Primary endpoint (weeks 9–12)				
Total abstinence from opioids and cocaine	60.6%	75.9%	2.05 (1.07, 3.90)	.03
Abstinence from opioids only	62.1%	77.3%	2.08 (1.10, 3.95)	.02
Abstinence from cocaine only	64.5%	82.4%	2.58 (1.37, 4.86)	.003
Secondary endpoint (weeks 0–12)				
Total one-third weeks abstinent	24.06 (11.89)	27.97 (8.17)		.02
Exploratory endpoint (weeks 5–12)				
Abstinence from opioids (weeks 7–12)	63.9%	78.2%	2.03 (1.09, 3.80)	.03
Abstinence from opioids (weeks 5–12)	68.5%	82.4%	2.16 (1.16, 4.01)	.01

Data are proportion of participants (%) or mean (SD).

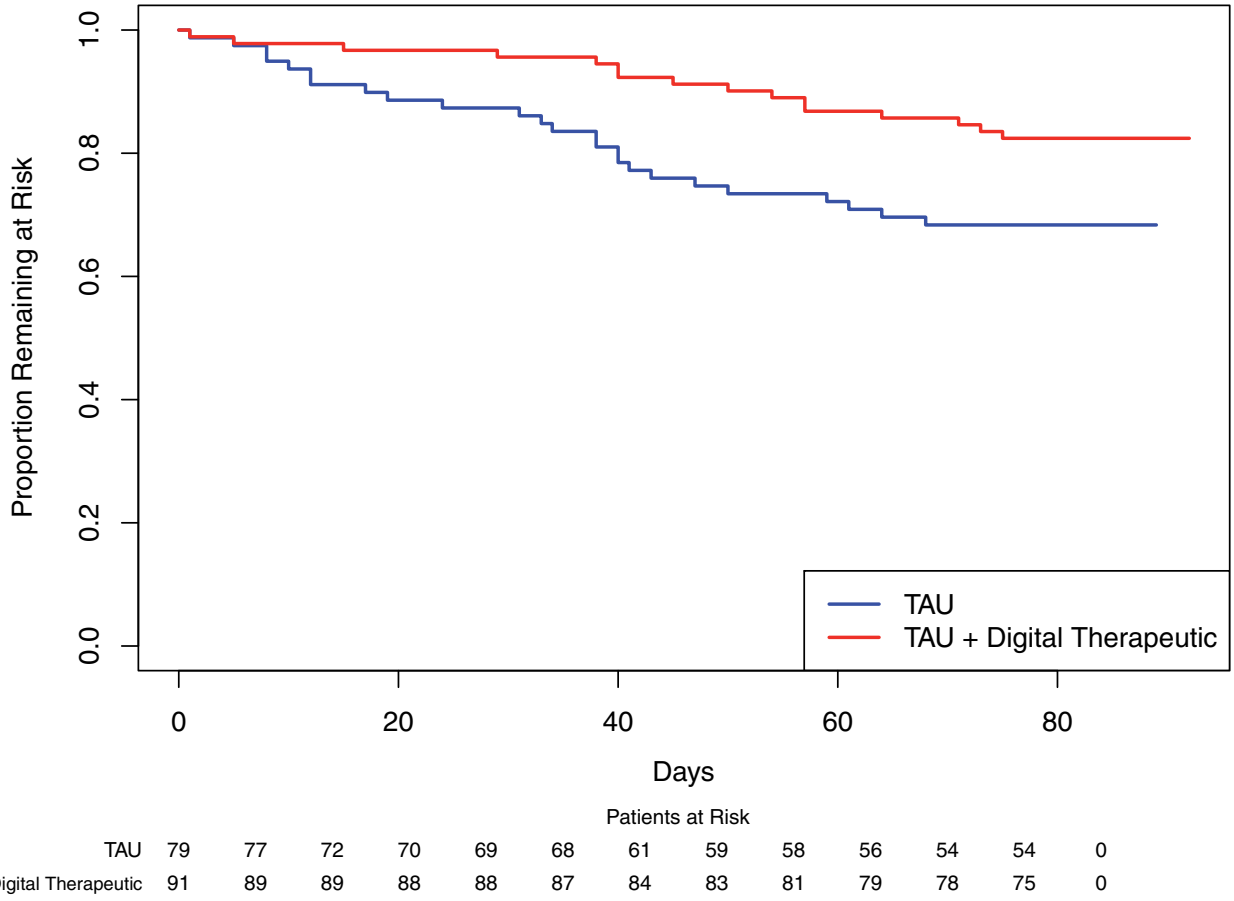

Figure 1. Kaplan-Meier estimates of time to withdrawal from treatment.

weeks of treatment, compared to those randomized to TAU (75.9 vs. 60.6%; OR 2.05, 95% CI 1.07–3.90; p=.03). Similar improvements were observed for abstinence from opioids only, with a 77.3% likelihood of abstinence during weeks 9–12 for the TAU plus PDT group vs. 62.1% for the TAU group (OR 2.08, 95% CI 1.10–3.95; p=.02). Likewise, 82.4% of participants randomized to TAU plus digital therapeutic were likely to be abstinent from cocaine only in weeks 9–12 compared to 64.5% for those randomized to TAU (OR 2.58, 95% CI 1.37–4.86; p=.003).

A significant improvement in retention during the study was observed, with a hazard ratio of 0.49 (95% CI 0.26–0.92; p=.02) in favor of the TAU plus digital therapeutic group (Figure 1). Treatment dropout rate was lower for the TAU plus digital therapeutic group (17.6%) compared to the TAU group (31.6%).

Secondary and exploratory endpoints

Total number of one-third weeks abstinent, and abstinence during the last 6 and 8 weeks of treatment are shown in Table 2. Participants randomized to TAU plus digital therapeutic achieved significantly more one-third weeks of abstinence (mean = 27.97, SD = 8.17) over the study duration compared to those randomized to TAU (mean = 24.06, SD = 11.89; p=.02). The TAU plus digital therapeutic group demonstrated a significantly increased likelihood of abstinence from opioids during the last 6 weeks of treatment compared to the TAU group (78.2 vs. 63.9%; OR 2.03, 95% CI 1.09–3.80; p=.03). Similarly, an increase in likelihood of abstinence was observed during the last 8 weeks of treatment, for participants who received TAU plus digital therapeutic compared to TAU (82.4 vs. 68.5%; OR 2.16, 95% CI 1.16–4.01; p=.01).

Table 3. Summary of adverse events.

Variable	TAU ($n = 79$)	TAU + digital therapeutic ($n = 91$)	Total ($n = 170$)	p Value
Participants reporting at least one adverse event	55 (69.6%)	57 (62.6%)	112 (65.9%)	.42
Adverse events[a]				
Gastrointestinal disorders	23 (29.1%)	23 (25.3%)	46 (27.1%)	
Musculoskeletal and connective tissue disorders	18 (22.8%)	18 (19.8%)	36 (21.2%)	
Psychiatric disorders	19 (24.1%)	17 (18.7%)	36 (21.2%)	
Nervous system disorders	13 (16.5%)	21 (23.1%)	34 (20.0%)	
General disorders and administration site conditions	11 (13.9%)	17 (18.7%)	28 (16.5%)	
Skin and subcutaneous tissue disorders	9 (11.4%)	8 (8.8%)	17 (10.0%)	
Infections and infestations	5 (6.3%)	8 (8.8%)	13 (7.6%)	
Investigations	3 (3.8%)	10 (11.0%)	13 (7.6%)	
Respiratory, thoracic and mediastinal disorders	5 (6.3%)	7 (7.7%)	12 (7.1%)	
Injury, poisoning and procedural complications	3 (3.8%)	4 (4.4%)	7 (4.1%)	
Eye disorders	1 (1.3%)	5 (5.5%)	6 (3.5%)	
Metabolism and nutrition disorders	1 (1.3%)	2 (2.2%)	3 (1.8%)	
Reproductive system and breast disorders	0	3 (3.3%)	3 (1.8%)	
Renal and urinary disorders	0	2 (2.2%)	2 (1.2%)	
Hepatobiliary disorders	0	1 (1.1%)	1 (0.6%)	
Pregnancy, puerperium and perinatal conditions	1 (1.3%)	0	1 (0.6%)	
Surgical and medical procedures	1 (1.3%)	0	1 (0.6%)	
Vascular disorders	0	1 (1.1%)	1 (0.6%)	

Data are n (%).
[a]Adverse events coded using preferred terms of the Medical Dictionary for Regulatory Activities (MedDRA) system organ classifications.

Participants randomized to TAU plus digital therapeutic completed a mean of 77.3 (SD = 32.36; range = 4–150) therapeutic modules (core + supplemental) over 12 weeks of treatment, including a mean of 42.2 (SD = 15.31; range = 4–78) core modules and a mean of 35.1 (SD = 17.59; range = 0–72) supplemental modules.

Safety

Observed adverse events were of the type and frequency anticipated in a population of patients with OUD (e.g. gastrointestinal, musculoskeletal, and psychiatric events) (Table 3). Overall, 112 participants reported an adverse event, including 57 (62.6%) in the TAU plus digital therapeutic group and 55 (69.9%) of the TAU participants. The proportion of participants reporting adverse events in each treatment group did not differ significantly (p=.42). No suicide-related events were reported. None of the adverse events observed were adjudicated to be device-related.

Discussion

In this secondary analysis, participants randomized to the TAU plus digital therapeutic group exhibited significant improvements in abstinence in the last 4 weeks of treatment and retention in treatment. These results were consistent regardless of whether abstinence was defined as opioids alone, cocaine alone, or both opioids and cocaine. Abstinence from opioids was also improved in participants who received TAU plus the digital therapeutic during the last 5–8 weeks of treatment. Time to withdrawal from treatment was extended significantly in the TAU plus digital therapeutic group compared to the TAU group, demonstrating improved treatment retention.

Substance use disorder is a chronic, refractory disease, characterized by lapses and relapses, requiring lifelong management[16]. OUD is a particular challenge, given the high rates of relapse and life-threatening consequences associated with opioid overdose[5]. Successful OUD treatment has been hampered by issues of access, especially to evidence-based medications and behavioral interventions, as well as stigma and poor treatment outcomes[21]. The therapeutic program evaluated in this study (and, by extension, reSET-O) may assist providers in addressing the opioid crisis, as it offers effective and accessible behavioral treatment. In particular, the way that the contingency management component of reSET-O is integrated into the therapeutic program and funded via the prescription cost, may address the observation that although CM has been shown to be very effective, it is often not implemented because of funding shortages or logistics at substance use disorder treatment centers[22].

The majority of individuals with substance use disorders consider abstinence an important aspect of recovery[23,24]. Improvements in short-term abstinence are predictive of long-term outcomes, and each additional day of abstinence may be life-saving given the risk of fatal opioid overdose[25,26]. The abstinence data presented here demonstrate that the PDT, when used in combination with buprenorphine MOUD, enabled a substantive improvement of a primary treatment objective, abstinence from opioid use. Furthermore, the PDT demonstrated a positive benefit/risk ratio, as improvement in the primary outcomes was observed without an increase in adverse events. This is seldom the case for pharmacotherapy and highlights the value of PDTs as a safe and effective treatment modality.

High treatment attrition rates (30% or higher) are still a major challenge facing OUD treatment providers and limit the effectiveness of care[27–29]. Many patients discontinue treatment within the first month[28,30,31]. Interventions to improve retention are much needed given the difficulty of keeping patients in treatment and the risks of relapse and overdose for those who discontinue. The finding that a digital therapeutic significantly improved treatment retention

further supports the value of incorporating such therapeutics into OUD treatment[21,26,32–34].

The data presented here were the basis for FDA market-authorization of reSET-O as a Class II medical device based on the predicate reSET, the first FDA market-authorized PDT for treating substance use disorder[19]. FDA market-authorization is important as it highlights independent review of safety and efficacy to support informed decision making by patients, healthcare payers and providers. There were 325,000 health and wellness apps available in 2017[35] – dozens related to substance use disorders. The majority of these apps are not clinically validated according to Good Clinical Practices, nor built according to Good Manufacturing Practices to ensure they function as intended. As a result, healthcare providers and patients have little guidance on which apps effectively treat OUD and should be integrated into clinical practice. Market-authorization by a regulatory body is the gold standard by which PDTs should be evaluated and on which labeling that clearly describes the indications and intended use of the therapeutic should be based.

Limitations

The present study has some limitations. The clinical trial was conducted at a single site, with a small sample of primarily Caucasian males. Thus, the sample may not be representative of all individuals seeking treatment for OUD. Abstinence rates were generally high in both treatment groups, which may have resulted from the combination of medication and CM for all participants and may have partially masked the impact of the PDT. The study was open-label, hence all parties were aware of the treatment interventions. However, an unblinded design is consistent with prior randomized studies assessing effectiveness of digital interventions for substance use disorders, in which participants and study staff are aware of the treatment assignment[10,12,15]. Finally, no follow-up of the participants was conducted subsequent to the 12-week intervention period, hence it is unclear how long participants may benefit after discontinuing treatment.

Conclusions

A digital therapeutic in combination with buprenorphine MOUD improves clinically significant patient outcomes including abstinence from illicit opioids and retention in treatment compared with treatment as usual. PDTs such as reSET-O may enhance treatment outcomes and clinical care, particularly in geographic regions without ready availability of clinics or trained staff, or in times when in-person access is limited, such as is the case with the current COVID-19 pandemic. Given the accessibility of mobile devices, reSET-O has the potential to meet many of the unmet needs in the current treatment delivery system for patients with OUD.

Transparency

Declaration of funding

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Declaration of financial/other relationships

YAM and HFL are employees of Pear Therapeutics. WKB is a principal of HealthSim, LLC; NotifiUS, LLC; BEAM Diagnostics, Inc; and Red 5 Group, LLC; serves on the scientific advisory board for Sober Grid, Inc.; Ria Health; and is a consultant for Alkermes, Inc.; Nektar Therapeutics; and Sandoz, Inc. LAM is affiliated with HealthSim, LLC; Red 5 Group, LLC; Square2 Square Systems, Inc. and is a scientific advisory board member of Pear Therapeutics. KG has no conflicts of interest to disclose. JB is a consultant of Pear Therapeutics. Peer reviewers on this manuscript have received an honorarium from CMRO for their review work but have no other relevant financial relationships to disclose.

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