Regence

Medical Policy Manual Medicine, Policy No. 175.02

Digital Therapeutic Products for Substance Use Disorders

Effective: November 1, 2023

Next Review: September 2024
Last Review: September 2023

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Digital health products are technologies, platforms, and systems that engage consumers for lifestyle, wellness, and health-related purposes. A digital therapeutic product is a specific type of digital health product that is practitioner-prescribed software that delivers evidence-based therapeutic intervention directly to a patient to prevent, manage, or treat a medical disorder or disease. Digital therapeutic products have been proposed to supplement or replace individual or group therapy and/or to deliver cognitive-behavioral therapy for the treatment of substance use disorders.

MEDICAL POLICY CRITERIA

Note:

- Member contracts for covered services vary. Member contract language takes precedence over medical policy.
- This policy does not address:
  - Software that is used for the function or control of an FDA-cleared or approved stand-alone medical device (e.g., external insulin pump or pacemaker).
  - Applications operated by a health care practitioner for remote health monitoring.

- Products not meeting the definition of a digital therapeutic (see Policy Guidelines in Digital Therapeutic Products, Medicine, Policy No. 175).

The use of a digital therapeutic product for the treatment of a substance use disorder, either as a stand-alone treatment or as an adjunct to standard treatment, is considered **investigational,** including but not limited to reSET® and reSET-O®.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

CROSS REFERENCES

1. Digital Therapeutic Products, Medicine, Policy No. 175

BACKGROUND

SUBSTANCE USE DISORDER

The American Psychiatric Association (APA) defines substance use disorder (SUD) as a complex condition "in which there is uncontrolled use of a substance despite harmful consequence. People with SUD have an intense focus on using a certain substance(s) such as alcohol, tobacco, or illicit drugs, to the point where the person's ability to function in day-to-day life becomes impaired."[1] The APA notes that individuals can become addicted to several substances including alcohol, marijuana, PCP, LSD and other hallucinogens, inhalants, opioids, sedatives, hypnotics, anxiolytics, cocaine, methamphetamine and other stimulants, and tobacco. The Diagnostic and Statistical Manual of Mental Disorders (DSM) details 11 problematic patterns of use that lead to clinically significant impairment or distress. Mild substance use disorder (SUD) is defined as meeting 2 to 3 criteria, moderate as 4 to 5 criteria, and severe as 6 or more criteria.

1. Often taken in larger amounts or over a longer period than was intended.
2. A persistent desire or unsuccessful efforts to cut down or control use.
3. A great deal of time is spent in activities necessary to obtain, use, or recover from the substance's effects.
4. Craving or a strong desire or urge to use the substance.
5. Recurrent use resulting in a failure to fulfill major role obligations at work, school, or home.
6. Continued use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by its effects.
7. Important social, occupational, or recreational activities are given up or reduced because of use.
8. Recurrent use in situations in which it is physically hazardous.
9. Continued use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance.
10. Tolerance.
11. Withdrawal.

TREATMENT

Treatments for drug addiction include behavioral counseling, skills training, medication, treatment for withdrawal symptoms, treatment for co-occurring mental health issues, and long-term follow-up to prevent relapse. For patients with primary opioid use disorder (OUD), medication-assisted treatment is the most common approach. U.S. Food and Drug Administration (FDA) approved drugs for opioid use treatment include a full opioid agonist (methadone), a partial opioid agonist (buprenorphine), and an opioid antagonist (naltrexone). These are used to suppress withdrawal symptoms and reduce cravings and may be used in combination with counseling and behavioral therapies.

One common psychosocial intervention is cognitive-behavioral therapy (CBT). CBT is an established therapy based on social learning theory that addresses a patient's thinking and behavior. CBT has proven positive effects for the treatment of SUD.[2] There are two main goals of CBT: first, recognize thoughts and behaviors that are associated with substance abuse, and second, expand the repertoire of effective coping responses. Specific goals for SUD and OUD include a better understanding of risk factors for use, more accurate attributions of cause and effect, increased belief in the ability to address problems, and coping skills. Specific skills may include motivation, drink/drug refusal skills, communication, coping with anger and depression, dealing with interpersonal problems, and managing stress.

The community reinforcement approach is a form of CBT that has a goal of making abstinence more rewarding than continued use. Community reinforcement approach increases non-drug reinforcement by teaching skills and encouraging behaviors that help improve employment status, family/social relations and recreational activities. Community reinforcement approach was originally developed for alcohol dependence and cocaine use and has been shown to be more effective than usual care in reducing the number of substance use days.

Contingency management may also be a component of addiction treatment. Contingency management, also known as motivational incentives, provides immediate positive reinforcement to encourage abstinence and attendance. Positive reinforcement may range from a verbal/text acknowledgement of completion of a task to monetary payment for drug-negative urine specimens. Contingency management is based on the principles of operant conditioning as formulated by B.F. Skinner, which posits that rewarding a behavior will increase the frequency of that behavior. Contingency management is typically used to augment a psychosocial treatment such as community reinforcement approach.

The combination of community reinforcement approach plus contingency management was shown in a 2018 network meta-analysis of 50 RCTs to be the most efficacious and accepted intervention among 12 structured psychosocial interventions, including contingency management alone, in individuals with cocaine or amphetamine addiction.[3] Positive reinforcement with voucher draws (eg, from a fishbowl) of variable worth that range from a congratulatory message to an occasional high dollar value are as effective as constant monetary vouchers. Studies conducted by the National Drug Abuse Treatment Clinical Trials Network have shown that intermittent reinforcement with incentives totaling $250 to $300 over 8 to 12 weeks both increases retention in a treatment program and reduces stimulant drug use during treatment.[4]

SOFTWARE AS A MEDICAL DEVICE

The International Medical Device Regulators Forum, a consortium of medical device regulators from around the world, which is led by the FDA, distinguishes between 1) software in a medical device and 2) software as a medical device (SaMD). The Forum defines SaMD as "software

that is intended to be used for one or more medical purposes that perform those purposes without being part of a hardware medical device".[5]

FDA's Center for Devices and Radiological Health is taking a risk-based approach to regulating SaMD. Medical software that "supports administrative functions, encourages a healthy lifestyle, serves as electronic patient records, assists in displaying or storing data, or provides limited clinical decision support, is no longer considered to be and regulated as a medical device".[6]

Regulatory review will focus on mobile medical apps that present a higher risk to patients.

- Notably, FDA will not enforce compliance for lower risk mobile apps such as those that address general wellness.
- FDA will also not address technologies that receive, transmit, store, or display data from medical devices.

The agency has launched a software pre-cert pilot program for SaMD that entered its test phase in 2019. Key features of the regulatory model include the approval of manufacturers prior to evaluation of a product, which is based on a standardized "Excellence Appraisal" of an organization, and its commitment to monitor product performance after introduction to the U.S. market. Criteria include excelling in software design, development, and validation. Companies that obtain pre-certification participate in a streamlined pre-market review of the SaMD. Pre-certified organizations might also be able to market lower-risk devices without additional review. In 2017, FDA selected nine companies to participate in the pilot program, including Pear Therapeutics. In September 2022, the Software Precertification (Pre-Cert) Pilot Program was completed with the issuance of the Report: The Software Precertification (Pre-Cert) Pilot Program: Tailored Total Product Lifecycle Approaches and Key Findings.[7] This document includes the following statement:

> Ultimately, the approach to regulating novel, swiftly-evolving medical device software must foster, not inhibit, innovation, while continuing to provide reasonable assurance of safety and effectiveness. These aspects are not mutually exclusive. A flexible, risk based approach to regulation could allow FDA to tailor regulatory requirements more efficiently for devices based on the latest science, the benefits and risks posed by devices, their real-world performance, and their contribution to promoting health equity. It could leverage the capabilities of evolving medical device software so that health care providers, patients, and users can benefit from advancement and innovation, and so that risk for such devices can be reduced through swift software and cybersecurity updates throughout the total product lifecycle, when needed. New legislative authority establishing such an approach could be supplemental to, and not replace, the established regulatory pathways.

REGULATORY STATUS

In 2017, reSET® (Pear Therapeutics), received De Novo marketing clearance from the FDA to provide CBT as an adjunct to contingency management, for patients with SUD who are enrolled in outpatient treatment under the supervision of a clinician (DEN160018). This was the first prescription digital therapeutic to be approved by the FDA. reSET® is indicated as a 12-week (90 days) prescription-only treatment intended to increase abstinence from a patient's substances of abuse during treatment and increase retention in the outpatient treatment. FDA product code: PWE.

In 2018, reSET-O® (Pear Therapeutics) was cleared for marketing by the FDA through the 510(k) pathway as a prescription-only digital therapeutic to “increase retention of patients with opioid use disorder (OUD) in outpatient treatment by providing cognitive behavioral therapy, as an adjunct to outpatient treatment that includes transmucosal buprenorphine and contingency management” (K173681). FDA determined that this device was substantially equivalent to existing devices. The predicate device was reSET®.

Vorvida® and Modia® (Orexo) provide support for individuals with problematic drinking and OUD. These digital technologies have not received marketing clearance by U.S. Food and Drug Administration and are not reviewed here. They are currently available in the U.S. through the Enforcement Policy for Digital Health Devices for Treating Psychiatric Disorders During COVID19. This guidance is intended to remain in effect until November 7, 2023 unless superseded by a revised final guidance before that date.[8]

EVIDENCE SUMMARY

Evidence reviews assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the length of life, quality of life, and ability to function including benefits and harms. Every clinical condition has specific outcomes that are important to patients and managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, two domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

DIGITAL HEALTH TECHNOLOGIES FOR SUBSTANCE USE DISORDER

Clinical Context and Therapy Purpose

Substance abuse is a serious health problem in the U.S. A 2019 survey from the Substance Abuse and Mental Health Services Administration found that 20.4 million people age 12 or older in the U.S., or 7.4 percent of the U.S. population, had substance use disorder (SUD), but only 1.5 million people were enrolled in substance use treatment.[9] The most common substances reported in the survey are alcohol, followed by tobacco and marijuana. Illicit drug use and prescription drug misuse occur in a lower percentage of the population.

A computer-delivered cognitive-behavioral therapy (CBT) program named CBT4CBT (Computer-Based Training for Cognitive Behavioral Therapy) has been developed to provide therapy for patients with substance abuse. The program includes seven core CBT skills delivered by on-screen narration, graphic animation, quizzes, and interactive exercises. In a

2018 RCT, both clinician and computer delivery of CBT reduced the frequency of substance use more than treatment as usual.[10] In addition, patients who received the computer-based CBT with minimal monitoring had the best treatment retention, learning of CBT concepts, and six-month outcomes compared to either clinician-delivered CBT or treatment as usual. A computer-based community reinforcement approach (CRA) plus vouchers was reported in a 2008 study to lead to similar levels of abstinence as patients who received clinician-guided CRA plus vouchers.[11] These results suggest that computerized CRA (CCRA) could potentially substitute for clinician-guided therapy and increase access to treatment.

In 2017 and 2018, the first prescription mobile apps (i.e., reSET® and reSET-O®) were cleared for marketing by the U.S. Food and Drug Administration (FDA). These have the potential to increase access to substance abuse treatments in patients who have SUD or OUD. These two apps are intended to provide CCRA as an addition to traditional therapy in the context of an outpatient program.

Evaluation of clinically meaningful outcomes

The outcome which is most frequently cited as the most important outcome for patients is abstinence from the substance of abuse.[12] This primary outcome should be measured during therapy, at the end of therapy, and at longer-term (e.g., 3, 6, and 12 months) follow-up to assess the durability of the treatment.

Other outcomes that have been reported as important to patients are drug craving, employment, and stable relationships. A semi-structured assessment of seven potential problem areas in substance-abusing patients is the Addiction Severity Index.[13] The domains are medical status, employment and support, drug use, alcohol use, legal status, family/social status, and psychiatric status. The Addiction Severity Index provides severity ratings of the client's need for treatment and composite scores which measure problem severity during the prior 30 days.

The Maudsley Addiction Profile is a brief standardized interview that assesses treatment outcomes in domains of substance abuse, health risk behavior, physical and psychological health, and personal social functioning.[14]

Retention in a treatment program is commonly used in addiction research but is an indirect measure of treatment success. Although retention is necessary, it is not sufficient to assess effectiveness and additional outcome measures are needed. Observational data from the Drug Abuse Treatment Outcome Studies suggest that most addicted individuals need at least three months in treatment to significantly reduce or stop their drug use and that the best outcomes occur in patients who participate in longer treatment.[15]

REVIEW OF EVIDENCE

Randomized Controlled Trials

The two pivotal RCTs for the prescription digital apps for substance use disorder (SUD) (resSET) and opioid use disorder (OUD) (reSET-O®) are described below and in Tables 1 and 2. The technology was developed by the National Institute of Drug Abuse-funded Center for Technology and Behavioral Health as the Therapeutic Education System, which was subsequently submitted to the FDA for a mobile platform by Pear Therapeutics.

Campbell (2014) reported the pivotal multicenter trial for reSET®, in which patients with SUD or OUD completed 20 to 30 minute multimedia modules on a desktop while in the clinic or at home.[16, 17] The active treatment was the Therapeutic Education System, which combined CCRA plus contingency management, and was compared to treatment as usual (therapy alone) at 10 community-based outpatient treatment programs as part of the National Drug Abuse Clinical Trials Network. Clinicians were able to access reports on computer activity and discussed module completion in the individual therapy sessions. Contingency management consisted of random selection of vouchers, which ranged from a congratulatory message to $100 cash, for module completion and negative urine drug results. The mean dollar earned was $277 (SD $226) over the 12 weeks. Although the study was intended to replace some of the hours of therapy, the Therapeutic Education System group received the same number of therapy session as the control group, so the combined program was effectively in addition to counseling alone.

The co-primary outcomes were abstinence from drug/heavy alcohol use in the last four weeks of treatment and retention in the treatment program. In the analysis by Campbell (2014),[16] the Therapeutic Education System reduced drop-out from the treatment program (hazard ratio = 0.72 [95% CI: 0.57 to 0.92], p=0.010), and the odds of achieving abstinence was 1.62 fold greater in the group with CCRA and contingency management group (p=0.010). However, the beneficial effect of the Therapeutic Education System was observed only in patients who were not abstinent at baseline. For patients who were abstinent at baseline, the Therapeutic Education System did not increase abstinence, and at three- and six-months follow-up, the effect of Therapeutic Education System was no longer significant. Subsequent analyses of the trial found that the Therapeutic Education System was not associated with improvements in social functioning compared to standard outpatient care.[18]

In the FDA analyses of the trial, results were analyzed for the entire cohort and for cohorts that excluded patients who reported opioid use.[17] Abstinence during weeks 9 to 12 and total abstinence with CCRA plus contingency management was significantly greater in the cohort as a whole and more so in the analyses that excluded primary opioid users. For example, abstinence during weeks 9 to 12 was 40.3% in the SUD subgroup who received CCRA plus vouchers compared to 17.6% in the group who received only therapy (p<0.001). Total abstinence, defined as the number of half weeks with a negative urine drug test, was 11.9 half weeks in the SUD subgroup who received the experimental treatment and 8.8 half weeks in controls (p=0.003).

In the pivotal study reported by Christensen (2014), CCRA was added to treatment as usual in patients who had opioids as the primary substance of abuse.[19, 20] Treatment as usual in this second trial included clinic visits three times per week with a reward for a negative urine drug screen (maximum of $997.50), sublingual buprenorphine/naloxone, and a clinician visit every two weeks. Patients who did not show up for any of the thrice weekly clinic visits were considered to have a positive drug screen and were considered drop-outs if they missed three visits in a row. The primary outcomes were the longest continuous abstinence and total abstinence. The study was powered to detect a three-week difference between groups in mean weeks of continuous abstinence. In the 84-day treatment program there were 9.7 more days of abstinence in the CCRA group (67.1 days) than in the control group (57.4 days, p=0.01). The trial did not meet one of the primary outcomes of a significant difference between the two groups in the longest abstinence (5.5 days p=0.214). The group using the computerized therapy had an increase in medication Addiction Severity Index scores (p=0.04) but did not show a significant improvement on the overall Addiction Severity Index (p>0.16).

The data on abstinence and Addiction Severity Index was not reported in the 510(K) Summary for the U.S. FDA.[20]

Both trials reported a significant increase in retention during the 12-week program. The SUD subgroup had a 23.8% drop out rate compared to 36.8% in the control group (p=0.004). The addition of CCRA to treatment as usual in patients with OUD also increased retention, with a hazard ratio for dropping out of treatment of 0.47 (0.26 to 0.85).

Both trials had limitations in relevance and in design and conduct that preclude determination of the effect of the intervention on relevant health outcomes, as is summarized in Tables 3 and 4.

- Studies were conducted with desktop computers, used primarily during clinic visits. In the study by Christensen (2014), CCRA was only available in the clinic to avoid confounding the efficacy of the program with compliance issues. Regular use of a mobile app without close supervision and outside of the constraints of a trial setting is unknown. Although a proposed benefit of digital technology is to increase access to evidence-based treatments, particularly in rural areas or where there are other limitations to specialist care, consistent use of a mobile device in the home and the resources and expertise of local providers to supervise addiction treatment is uncertain.

- In the study by Campbell (2014), the experimental group received both the web-based CCRA and a reward for a negative drug test. The trial was designed to assess the combined treatment approach, and not specifically the CCRA program. Because a reward for a negative drug screen is known by itself to increase both retention and abstinence during a trial,[4] the contribution of the digital technology to the increase in abstinence in patients with SUD cannot be determined. Notably, abstinence was not improved at the three and six-month follow-up, raising further questions about whether the increase in abstinence during the trial was due to contingency management rather than the CCRA.

- The choice (e.g., retention) and timing (e.g., during treatment) of the outcome measures. Abstinence after a treatment program is a main objective of therapy. Abstinence was greater during the trial, but not improved at the three and six-month follow-up.

- The potential for performance bias inunblinded studies. Nearly half of patients who qualified for the study chose not to participate. There may have been greater motivation to use the new technology in patients who agreed to participate in the study. While acknowledging the difficulty of blinding with this type of intervention, providing a control intervention of similar intensity, such as computer time that is not based on CRA, is feasible.

Additional data from well-designed trials are needed to determine the effects of the technology on addiction.

Table 1. Summary of Key RCT Characteristics

Study; Trial	Countries	Sites	Participants	Interventions	
				Active[a]	***Comparator***
Campbell (2014) FDA Submission DEN160018[16, 17]	U.S.	10	507 adult patients with self-report of drug use, with a subset of 305 who did not have primary use of opioids treated at community health centers	12 weeks of treatment as usual + CCRA (62 modules on a desktop) + contingency management for module completion and negative drug screen (n=255)	12 weeks of treatment as usual consisting ≥ 2 individual or group therapy sessions per week (n=252)
Christensen (2014) FDA summary K173681[19, 20]	U.S.	1	170 opioid-dependent adults	12 weeks of CCRA (69 modules on a desktop in the clinic) + contingency management + buprenorphine/ naloxone (n=92)	12 weeks of contingency management + buprenorphine/ naloxone (n=78)

CCRA: computer-based community reinforcement approach; RCT: randomized controlled trial.
[a]CCRA consisted of 20 to 30 min multimedia computer modules. Patients completed a mean of 36.6 (standard deviation, 18.1) out of 62 total CCRA modules in the study by Campbell et al. There were a total of 69 CCRA modules in the study by Christensen et al.

Table 2. Summary of Key RCT Results

Study	Abstinence		Total Abstinence		Retention		Dropping Out of Treatment		ASI overall	ASI Medication Subscale
Campbell (2014) FDA Submission DEN160018[16, 17]	Rate During Weeks 9-12		Half weeks							
	Entire Cohort (n=507)	***Excluding Primary Opioid Abusers (n=399)***	***Entire Cohort (n=507)***	***Excluding Primary Opioid Abusers (n=399)***	***Entire Cohort (n=507)***	***Excluding Primary Opioid Abusers (n=399)***	***Entire Cohort (n=507)***	***Excluding Primary Opioid Abusers (n=399)***		
Treatment as usual + CCRA + contingency management	29.7%	40.3%	10.9	11.9	72.2%	76.2%	27.8%	23.8%		
Treatment as usual	16.0%	17.6%	8.6	8.8	63.5%	63.2%	36.5%	36.8%		
p	0.008	<0.001	0.002	0.003			0.03	0.004		

Study	Abstinence	Total Abstinence	Retention	Dropping Out of Treatment	ASI overall	ASI Medication Subscale
Christensen (2014) K173681[19, 20]	Longest Abstinence in Days (+ SD)	Total Days + SD	Treatment Completion			
CRA + contingency management	55	67.1 + 19.3	80.4%	17.6%		
Contingency management	49.5	57.4 + 28.0	64.1%	31.6%		
HR/Diff/OR (95% CI)	Diff: 5.5	Diff: 9.7 (2.3 to 17.2)	OR: 2.30 (1.15 to 4.60)	HR: 0.47 (0.26 to 0.85)		
p	0.214	0.011		0.0224	>0.24	0.04

ASI: Addiction Severity Index; CI: confidence interval; (C)CRA: (computer-based) community reinforcement approach; HR: hazard ratio; OR: odds ratio; RCT: randomized controlled trial; SD: standard deviation.

Table 3. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Campbell (2014); FDA Submission DEN16001[16, 17]	4. The study volunteers may not be representative of the general population with substance use disorder.	2. Was an earlier desktop technology and was conducted mostly in the clinic	3. The comparator did not include contingency management with vouchers. Delivery was not a similar intensity as the intervention.	1. Uncertain significance of retention as an outcome. 5. The minimal clinically important difference for abstinence was not pre-specified	1. Duration of follow-up not sufficient to assess durability.
Christensen (2014) K173681[19, 20]		2. Was an earlier desktop technology and was conducted in the clinic	3. Delivery was not a similar intensity as the intervention.	1. Uncertain significance of retention as an outcome. 5. The minimal clinically important difference for abstinence was not pre-specified.	1. The study did not extend after 12 week treatment period, limiting inferences on efficacy for abstinence.

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4.Not the intervention of interest.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 4. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Campbell (2014); FDA Submission DEN160018[16, 17]		1. Participants and investigators were not blinded to treatment assignment.	2. Subgroup analyses in the FDA Summary were not pre-specified			
Christensen (2014) K173681[19, 20]		1. Participants and investigators were not blinded to treatment assignment.	2. Data on abstinence was not included in the FDA Summary			

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.
[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.
[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

OBSERVATIONAL STUDIES

Xiong (2023) published the results of an industry-funded analysis of reSET® data from 602 patients with substance use disorder who filled a 12-week prescription of the software.[21] Patients were prescribed 61 therapy sessions and contingency management rewards (e.g., positive reinforcement message or monetary gift cards) based on lesson completion and negative urine drug screens. The reSET® application collected data on engagement (defined as any activity in the prescription digital therapeutic), retention (any activity in weeks 9 to 12), and self-reported substance use data. Participants were included in data analysis if they completed at least one therapy session. 52% of patients completed all core modules, and median lessons completed was 33 (out of 61 possible). Retention during treatment in the last four weeks of treatment was 74%. Substances used by patients, as reported by clinicians, were alcohol (46.7%), opioids (17.9%), stimulants other than cocaine (13.3%), cannabis (7.8%), cocaine (6.5%), and other/unknown (7.8%). 434 patients (72%) provided at least one substance use self-report during weeks 9 to 12. 92 patients (15%) had at least one clinician-reported urine drug screening during weeks 9 to 12. Abstinence was calculated as a combined measure of urine drug screening and self-reporting. Based on this metric, the authors reported that 434 patients (86%) were abstinent.

In a retrospective analysis of data from the Campbell pivotal trial, Luderer (2022) reported an association between engagement with the app (i.e., total number of modules completed) and abstinence during weeks 9 to 12 among the157 study completers (OR = 1.11; 95% CI 1.08-1.14).[22]Maricich (2022) published the results of a secondary analysis of data from the trial, excluding participants with OUD. The data included were from 399 individuals with SUD related to alcohol, cannabis, cocaine, or other stimulants; 206 were in the digital therapeutic group and were 193 in the treatment as usual group.[23] Abstinence was significantly higher than treatment as usual in the reSET® group (40.3% vs. 17.6%; $p<0.001$) as was retention in therapy (76.2% vs. 63.2%; $p=0.004$).

Marichich (2021) performed an industry-funded analysis of reSET-O® data from 3144 patients with OUD who had filled a 12-week prescription of the software.[24] Participants were instructed to complete at least four modules per week with a total possible of 31 core modules and 36 supplemental modules. Analysis of the software's data showed that about half of the patients completed all 31 modules, 66% completed half of the modules, and 74% of patients actively participated through 12 weeks. Use decreased from 100% in the first week to 55% of individuals completing 4 modules in week 12. (Retention in the pivotal study by Christensen was 80% for the software compared to 64% for contingency management alone).

Abstinence during the last four weeks of treatment was determined by either urine drug screening or self-report recorded on reSET-O®. With a conservative estimate of missing data considered to be a positive drug screen, 66% of patients were estimated to be abstinent during the last four weeks of the prescription. For patients who completed 3 to 5 modules in the first week, abstinence in the final four weeks ranged from 83% to 89%. A limitation of this study is that patients who completed more modules in the first week may have been more motivated to remain abstinent, and cause and effect cannot be determined from this non-comparative observational study.

Marichich (2021) also published data from a subset of 643 individuals from the above cohort who completed the 12-week prescription and were then prescribed a second 12-week refill

prescription.[25] At the end of the second prescription period, 86.0% of the cohort were abstinent and 91.4% were retained in treatment through 24 weeks.

SUMMARY OF EVIDENCE

For individuals with SUD other than OUD who receive a prescription digital therapeutic, the evidence includes one pivotal RCT and secondary analyses of data from the trial. Relevant outcomes are symptoms, morbid events, change in disease status, quality of life, and medication use. Mobile digital technology is proposed as an adjunct to outpatient treatment; however, there are several limitations in the current evidence base that limit any conclusions regarding efficacy. The RCT assessed the combined intervention of computer-based learning and a reward for abstinence. Since reward for abstinence alone has been shown to increase both abstinence and retention, the contribution of the web-based program to the overall treatment effect cannot be determined. The treatment effect on abstinence was not observed at follow-up, raising further questions about the relative effects of the rewards and the web program. While the RCT reported a positive effect on the intermediate outcome of retention, the relationship between retention and relevant health outcomes in this trial is uncertain. A secondary analysis of data from the trial reported an association between engagement with the app and abstinence at 9 to 12 weeks, but study design limitations preclude drawing conclusions from this study. Given these limitations, further study in well-designed trials is needed to determine the effects of prescription digital therapeutics on relevant outcomes in individuals with SUD. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with OUD who receive a prescription digital therapeutic, the evidence includes one pivotal RCT and analysis of data of more than 3000 patients from the mobile app. Relevant outcomes are symptoms, morbid events, change in disease status, quality of life, and medication use. Mobile digital technology is proposed as an adjunct to outpatient treatment that includes transmucosal buprenorphine and contingency management; however, there are a number of limitations in the current evidence base that limit any conclusions regarding efficacy. The RCT did not meet a primary objective of longest days of abstinence. While there was a positive effect on the intermediate outcome of retention, the relationship between retention and relevant health outcomes in this trial is uncertain. Retrospective observational studies found that participants who completed more modules with the mobile app had greater abstinence during weeks 9 to 12 and, in a subgroup of individuals who received a refill prescription, during weeks 21 to 24, but the retrospective design and lack of a control group with comparable motivation limits interpretation of these results. Given these limitations, further study in well-designed trials is needed to determine the effects of prescription digital therapeutics on relevant outcomes in individuals with OUD. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

PRACTICE GUIDELINE SUMMARY

AMERICAN SOCIETY OF ADDICTION MEDICINE

In 2020, the American Society of Addiction Medicine (ASAM) published a focused update of their National Practice Guideline for the Treatment of Opioid Use Disorder.[26] The guideline recommends that psychosocial treatment be considered in conjunction with pharmacological treatment for opioid use disorder and notes, "At a minimum, the psychosocial treatment component of the overall treatment program should include assessment of psychosocial needs; individual and/or group counseling; linkages to existing support systems; and referrals

to community-based services." The guideline also notes that "psychosocial treatment may also include more intensive individual counseling and psychotherapy, contingency management, and mental health services" and, "while questions remain about which specific psychosocial therapies work best with which pharmacological treatments, there is widespread support for recommending psychosocial treatment as an important component of a patient's opioid use disorder treatment plan." The guideline does not address digital therapies.

NATIONAL INSTITUTE ON DRUG ABUSE

The 2018 Principles of Drug Addiction and Treatment from the National Institute on Drug Abuse describes evidence-based approaches to drug addiction treatment.[15] Behavioral therapies include cognitive-behavioral therapy (alcohol, marijuana, cocaine, methamphetamine, nicotine), contingency management (alcohol, stimulants, opioids, marijuana, nicotine), community reinforcement approach plus vouchers (alcohol, cocaine, opioids), motivational enhancement therapy (alcohol, marijuana, nicotine), the matrix model (stimulants), 12-step facilitation therapy (alcohol, stimulants, opiates) and family behavior therapy. The guideline does not address digital therapies for substance use disorders.

SUMMARY

There is not enough research to show that digital therapeutic products for the treatment of substance use disorders improves net health outcomes. No clinical guidelines based on research recommend digital therapeutic products for the treatment of substance use disorders. Therefore, digital therapeutic products for the treatment of substance use disorders are considered investigational.

REFERENCES

1. The American Psychiatric Association: What Is a Substance Use Disorder? 12/2020 [cited 9/21/2023]. 'Available from:' https://www.psychiatry.org/patients-families/addiction/what-is-addiction.
2. McHugh RK, Hearon BA, Otto MW. Cognitive behavioral therapy for substance use disorders. *Psychiatr Clin North Am.* 2010;33(3):511-25. PMID: 20599130
3. De Crescenzo F, Ciabattini M, D'Alo GL, et al. Comparative efficacy and acceptability of psychosocial interventions for individuals with cocaine and amphetamine addiction: A systematic review and network meta-analysis. *PLoS Med.* 2018;15(12):e1002715. PMID: 30586362
4. Stitzer ML, Petry NM, Peirce J. Motivational incentives research in the National Drug Abuse Treatment Clinical Trials Network. *J Subst Abuse Treat.* 2010;38 Suppl 1:S61-9. PMID: 20307797
5. International Medical Device Regulators Forum. Software as a Medical Device (SaMD): Key Definitions. 2013. [cited 9/21/2023]. 'Available from:' http://www.imdrf.org/docs/imdrf/final/technical/imdrf-tech-131209-samd-key-definitions-140901.pdf.
6. U.S. Food and Drug Administration. Digital health innovation action plan. [cited 9/21/2023]. 'Available from:' https://www.fda.gov/media/106331/download.
7. Digital Health Software Precertification (Pre-Cert) Program. U.S. Food and Drug Administration (FDA). [cited 9/21/2023]. 'Available from:' https://www.fda.gov/medical-

devices/digital-health-center-excellence/digital-health-software-precertification-pre-cert-pilot-program.
8. U.S. Food and Drug Administration. Enforcement policy for digital health devices for treating psychiatric disorders during the coronovirus disease 2019 (COVID-19) public health emergency. Guidance for industry and Food and Drug Administration Staff. [cited 9/25/2023]. 'Available from:' https://www.fda.gov/media/136939/download.
9. U.S. Department of Health and Human Services, Substance Abuse and Mental Health Services Administration. Data and Dissemination. [cited 9/21/2023]. 'Available from:' https://www.samhsa.gov/data.
10. Kiluk BD, Nich C, Buck MB, et al. Randomized Clinical Trial of Computerized and Clinician-Delivered CBT in Comparison With Standard Outpatient Treatment for Substance Use Disorders: Primary Within-Treatment and Follow-Up Outcomes. *Am J Psychiatry.* 2018;175(9):853-63. PMID: 29792052
11. Bickel WK, Marsch LA, Buchhalter AR, et al. Computerized behavior therapy for opioid-dependent outpatients: a randomized controlled trial. *Exp Clin Psychopharmacol.* 2008;16(2):132-43. PMID: 18489017
12. Dennis BB, Sanger N, Bawor M, et al. A call for consensus in defining efficacy in clinical trials for opioid addiction: combined results from a systematic review and qualitative study in patients receiving pharmacological assisted therapy for opioid use disorder. *Trials.* 2020;21(1):30. PMID: 31907000
13. Denis CM, Cacciola JS, Alterman AI. Addiction Severity Index (ASI) summary scores: comparison of the Recent Status Scores of the ASI-6 and the Composite Scores of the ASI-5. *J Subst Abuse Treat.* 2013;45(5):444-50. PMID: 23886822
14. Marsden J, Gossop M, Stewart D, et al. The Maudsley Addiction Profile (MAP): a brief instrument for assessing treatment outcome. *Addiction.* 1998;93(12):1857-67. PMID: 9926574
15. National Institute on Drug Abuse. Principles of Drug Addiction Treatment: A Research-Based Guide (Third Edition). 2018. [cited 09/21/2023]. 'Available from:' https://nida.nih.gov/sites/default/files/675-principles-of-drug-addiction-treatment-a-research-based-guide-third-edition.pdf.
16. 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. PMID: 24700332
17. U.S. Food and Drug Administration. De Novo Classification Request for reSET. [cited 9/21/2023]. 'Available from:' https://www.accessdata.fda.gov/cdrh_docs/reviews/DEN160018.pdf.
18. Marino LA, Campbell ANC, Pavlicova M, et al. Social functioning outcomes among individuals with substance use disorders receiving internet-delivered community reinforcement approach. *Subst Use Misuse.* 2019;54(7):1067-74. PMID: 30849925
19. 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. PMID: 25090043
20. U.S. Food and Drug Administration. 510K Summary. 2019. [cited 09/21/2023]. 'Available from:' https://www.accessdata.fda.gov/cdrh_docs/pdf17/K173681.pdf.
21. Xiong X, Braun S, Stitzer M, et al. Evaluation of real-world outcomes associated with use of a prescription digital therapeutic to treat substance use disorders. *Am J Addict.* 2023;32(1):24-31. PMID: 36264211

22. Luderer HF, Campbell ANC, Nunes EV, et al. Engagement patterns with a digital therapeutic for substance use disorders: Correlations with abstinence outcomes. *J Subst Abuse Treat.* 2022;132:108585. PMID: 34366201
23. Maricich YA, Nunes EV, Campbell ANC, et al. Safety and efficacy of a digital therapeutic for substance use disorder: Secondary analysis of data from a NIDA clinical trials network study. *Subst Abus.* 2022;43(1):937-42. PMID: 35420979
24. Maricich YA, Xiong X, Gerwien R, et al. Real-world evidence for a prescription digital therapeutic to treat opioid use disorder. *Curr Med Res Opin.* 2021;37(2):175-83. PMID: 33140981
25. Maricich YA, Gerwien R, Kuo A, et al. Real-world use and clinical outcomes after 24 weeks of treatment with a prescription digital therapeutic for opioid use disorder. *Hosp Pract (1995).* 2021;49(5):348-55. PMID: 34461801
26. The ASAM National Practice Guideline for the Treatment of Opioid Use Disorder: 2020 Focused Update. *J Addict Med.* 2020;14(2S Suppl 1):1-91. PMID: 32511106

CODES

NOTE: Not all digital health products will have a specific code. These are examples of codes that may be relevant.

Codes	Number	Description
CPT	0702T	~~Remote therapeutic monitoring of a standardized online digital cognitive behavioral therapy program ordered by a physician or other qualified health care professional; supply and technical support, per 30 days~~ (Deleted 01/01/2023)
	0703T	~~;management services by physician or other qualified health care professional, per calendar month~~ (Deleted 01/01/2023)
	98978	Remote therapeutic monitoring (eg, therapy adherence, therapy response); device(s) supply with scheduled (eg, daily) recording(s) and/or programmed alert(s) transmission to monitor cognitive behavioral therapy, each 30 days
	99199	Unlisted special service, procedure or report [when specified as a digital health management software application]
HCPCS	A9291	Prescription digital behavioral therapy, fda cleared, per course of treatment
	E1399	Durable medical equipment, miscellaneous [when specified as a digital health management software application]

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