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Prescription Digital Therapeutics

Clinical Policy Bulletins | Medical Clinical Policy Bulletins

Number: 0999

Policy

Aetna considers the following prescription digital therapeutics (PDTs) experimental and investigational because there is insufficient evidence in the published peer-reviewed literature to support their effectiveness:

- BlueStar Rx
- Canvas Dx
- d-Nav
- Endeavor Rx
- Freespira
- Halo AF Detection System
- Insulia
- leva Pelvic Health System
- Nerivio
- NightWare
- reSET
- reSET-O
- Somryst.

Background

Policy History

Effective: 01/07/2022

Next Review: 11/10/2022

Definitions

Additional Information

Clinical Policy Bulletin Notes

With the rapid advancement of technology in healthcare, there has been an increase in the growth of software technologies created for the purpose of improving healthcare delivery. The U.S. Food and Drug Administration (FDA) refers to these as “device software functions,” a category of software that also includes mobile medical applications (MMAs), which may be deployed on various platforms (e.g., mobile platforms, other general-purpose computing platforms, or in the operation or control of a hardware device), and are designed to enable consumers to better manage their health and well-being, assist healthcare providers to improve and facilitate patient care, diagnose a condition, or trigger a command necessitating patient action. Some examples of the previously mentioned MMA functionalities include the Radiation Emergency Medical Management (REMM) app and the National Institute of Health's LactMed (FDA, 2021b).

Although the FDA encourages the development of MMAs with the intention to improve healthcare and to provide consumers and healthcare practitioners useful information, the FDA recognizes its public health responsibility in the provision of oversight to ensure the safety and effectiveness of such device software functions. To provide guidance and a framework in the evaluation and review of the clinical evidence, safety, and efficacy of device software functions and MMAs, the International Medical Device Regulators Forum (IMDRF), directed by the FDA, states that medical purpose software consists of (i) software in a medical device and (ii) software as a medical device (SaMD) (IMDRF, 2021). Additionally, the Center for Devices and Radiological Health, which functions within the FDA, takes a customized, risk-based approach with a priority on the subset of software functions that qualify under the regulatory definition of "device" and ensure those that have a potentially greater risk must require FDA review (FDA, 2021f). Furthermore, software functions that the FDA specifies as device software functions requiring regulatory oversight include:

- "Software functions that are an extension of one or more medical devices by connecting to such a device(s) for purposes of controlling the device(s) or analyzing medical device data"; or
- "Software functions (typically, mobile apps) that transform the mobile platform into a regulated medical device by using

attachments, display screens, or sensors or by including functionalities similar to those of currently regulated medical devices. Software functions that use attachments, display screens, sensors or other such similar components to transform a mobile platform into a regulated medical device are required to comply with the device classification associated with the transformed platform"; or

- "Software functions that become a regulated medical device by performing patient-specific analysis and providing patient-specific diagnosis, or treatment recommendations. These types of functions are similar to or perform the same function as those types of software devices that have been previously cleared or approved".

The FDA will not require manufacturers to submit premarket review applications or registration their software with the FDA for software functions that qualify under the regulatory definition of a "device" when such software functions pose a minimal risk to patients and consumers. Software functions that belong to this FDA discretionary approach include functions that are as follows (FDA, 2021f):

- "Help patients (i.e., users) self-manage their disease or conditions without providing specific treatment or treatment suggestions"; or
- "Automate simple tasks for healthcare providers".

More recently, a novel therapeutic class referred to as prescription digital therapeutics (PDTs) have entered into the digital healthcare space. This therapeutic class is different from other traditional health and wellness apps in that it possesses the following unique characteristics (Digital Therapeutics Alliance, 2021):

- PDTs deliver evidence-based and high quality software-driven therapeutic interventions that diagnose, prevent, manage, or treat a medical disorder or disease independently or in combination with medications, devices, or other treatments to optimize patient care and health outcomes; and
- PDTs are authorized by the FDA (i.e., cleared or approved) with approved directions for use; and

- PDTs undergo rigorous evaluation for safety and effectiveness in clinical trials with clinically-meaningful results published in peer-reviewed journals; and
- PDTs are prescribed and initiated by a qualified and licensed healthcare practitioner.

In order to provide regulatory oversight for software-based medical devices that is both streamlined and efficient, the FDA launched the Pre-Cert Pilot Program test phase in 2019. "In the Pre-Cert program, the FDA is proposing that software products from precertified companies would continue to meet the same safety and effectiveness standard that the agency expects for products that have followed the traditional path to market." A proposed aim is to focus on the software developer or digital health technology developer, rather than mainly on the product. Additionally, "the FDA's Total Product Lifecyle (TPLC) approach enables the evaluation and monitoring of a software product from its premarket development to postmarket performance, along with continued demonstration of the organization's excellence." Proposed key components of the FDA's TPLC methodology include the following (FDA, 2021d):

- "Excellence Appraisal: Identifying the objective criteria and methodology that the FDA will use to pre-certify a company and decide whether a company can keep its precertification status."
- "Review Determination: Developing a risk-based framework so a precertified company can determine the premarket review pathway for their products. Potentially precertified companies could market their lower-risk devices without the FDA's premarket review or only a streamlined premarket review based on the company's precertification level and International Medical Device Regulators Forum (IMDRF) risk categorization."
- "Streamlined Review: Identifying the type of information that a precertified company would include in its premarket submission for the FDA to review software products for safety and effectiveness before patients access them."
- "Real-world Performance: Identifying the type of information that may be available to or accessibly by a precertified company about how its software product is performing with patients to support

the regulatory status of the product and new and evolving product functions."

In September 2017, the following 9 companies out of over 100 candidates were chosen by the FDA to participate in the development of the Software Pre-Cert Pilot Program: Apple, Fitbit, Johnson & Johnson, Pear Therapeutics, Phosphorous, Roche, Samsung, Tidepool, and Verily (FDA, 2021d).

Other professional organizations such as the American Medical Association, American Psychiatric Association, and the Academy of Managed Care Pharmacy are also beginning to develop a framework and provide guidance to healthcare practitioners as they begin to integrate mobile health technologies, mobile apps, and digital therapeutics as a component in the delivery of patient care.

BlueStar Rx

WellDoc (Columbia, MD) developed the BlueStar Rx System which is indicated for use by healthcare providers and their patients who are 18 years of age and older to aid in their self-management of type 1 or type 2 diabetes. The BlueStar Rx System is an FDA-cleared software app that is complimentary to the patient's current therapies (e.g., pharmacologic, diet, exercise, and counseling). Patients can use the mobile app or the web version of BlueStar. The software app includes an always-on, fully-automated software coach that sends a report to the patient's healthcare provider team via facsimile, email, or electronic medical record and a patient portal is managed by an administrator who can manage, review, report, survey and communicate with the patient. In addition to reporting blood glucose results and supporting medication adherence, the BlueStar Rx System delivers coaching messages based on current time blood glucose results and trends. A prescription is required by a licensed healthcare professional for the BlueStar Rx system which also includes an insulin dose calculator that enables patients to use their prescribed regimen to determine insulin dosage based on a given amount of carbohydrates and/or blood glucose values. WellDoc states on their website that "The BlueStar Rx System is not intended to replace the care

provided by a licensed healthcare professional, including prescriptions, diagnosis, or treatment" (Digital Therapeutics Alliance, 2021b; WellDoc, 2021).

Quinn and colleagues (2011) conducted the Mobile Diabetes Intervention Study, a cluster-randomized clinical trial to assess whether the addition of mobile application coaching and patient/provider web portals to community primary care compared to standard diabetes management would decrease glycosylated hemoglobin levels in patients with type 2 diabetes. This study randomly assigned 26 primary care practices consisting of 163 participants to one of three stepped treatment groups or a control group (usual care). The primary outcome was a change in glycated hemoglobin levels over a 1-year treatment duration and secondary outcomes included changes in patient-reported diabetes symptoms, diabetes distress, depression, and other clinical (blood pressure) and laboratory (lipid) values. Maximal treatment included a mobile- and web-based self-management patient coaching system and provider decision support. Automated, real-time educational and behavioral messaging were sent to patients via mobile phone in response to individually analyzed blood glucose results, diabetes medications, and lifestyle behaviors. Quarterly summary reports regarding patient's glycemic control, diabetes medication management, lifestyle behaviors, and evidence-based treatment options were sent out to providers. Results included 1.9% mean declines in glycated hemoglobin in the maximal treatment group and 0.7% in the usual care group, a difference of 1.2% ($p<0.001$) over 12 months. Significant differences were not noticeable between groups for patient-reported diabetes distress, depression, diabetes symptoms, or blood pressure and lipid levels (all $p>0.05$). The investigators concluded that the combination of behavioral mobile coaching with blood glucose data, lifestyle behaviors, and patient self-management data individually evaluated and presented with evidence-based guidelines to providers significantly decreased glycosylated hemoglobin levels over 1 year.

Agarwal and colleagues (2019) evaluated BlueStar mobile app, an FDA-approved mobile prescription therapy, to determine if app usage results in improved hemoglobin A_{1c} (HbA_{1c}) for diverse participants in real-life clinical contexts. The study involved of a multicenter pragmatic randomized controlled trial consisting of 110 participants randomized to

the immediate treatment group (ITG) receiving the intervention for 6 months, and 113 participants randomized to the wait-list control (WLC) group receiving usual care for the first 3 months and then receiving the intervention for 3 months. The primary outcome was glucose control measured by HbA_{1c} levels at 3 months and secondary outcomes determined intervention impact on patient self-management, experience of care, and self-reported health utilization using validated scales (i.e., the Problem areas in Diabetes, the Summary of Diabetes Self-Care Activities, and the EuroQo1-5D). The BlueStar mobile app captured the intervention usage data. The results did not show evidence of intervention impact on HbA_{1c} levels at 3 months (mean difference [ITG-WLC] -0.42, 95% Confidence Interval [CI] -1.05 to 0.21; p=0.19). Additionally, no intervention effect on secondary outcomes measuring diabetes self-efficacy, quality of life, and healthcare utilization behaviors were observed. Significant variation in app usage by site was noted such that participants from one site logged in to the app a median of 36 days over 14 weeks (interquartile range [IQR] 10.5-124), whereas participants at another site showed a notable decrease in app usage (median 9; IQR 6-51). The investigators concluded that there was no difference between intervention and control arms for the primary outcome of glycemic control measured by HbA_{1c} levels and the low usage of the app among participants warrants further study of patient and site-specific factors that increase app usage.

Canvas Dx

Cognoa (Palo Alto, CA) developed Canvas Dx which is an FDA-cleared software medical device that is indicated for use by healthcare providers as an aid in the diagnosis of Autism Spectrum Disorder (ASD) for patients ages 18 months through 72 months who are at risk for developmental delay based on concerns of a parent, caregiver, or healthcare provider. Canvas Dx utilizes a clinically validated artificial intelligence (AI) technology that integrates three separate user-friendly inputs. The inputs include a parent/caregiver questionnaire regarding the child's behavior and development collected via a parent/caregiver facing app, a questionnaire completed by a video analyst who reviews parent/caregiver recorded videos of the child, and a healthcare provider questionnaire completed by a physician during child and parent/caregiver interaction via a healthcare provider portal. A device output is then generated after an

algorithm evaluates all of these inputs which will be used by the physician in addition to their clinical judgement. The device is by prescription only and Cognoa states on the www.canvasdx.com website "The device is not intended for use as a stand-alone diagnostic device but as an adjunct to the diagnostic process" (Canvas Dx, 2021; Cognoa, 2021).

Abbas and colleagues (2017) applied machine learning (ML) to gold standard clinical data captured across thousands of children at-risk for autism spectrum disorder to develop a low-cost, quick, and easy to use autism screening tool. Two algorithms to identify autism, included one based on short, structured parent-reported questionnaires and short, semi-structured home videos of children identifying key behaviors which are then combined in an algorithm to yield a single assessment of higher accuracy. The performance of these algorithms and their combination was assessed in a multicenter clinical study comprised of 162 children. While significant accuracy improvement compared to standard screening tools in measurements of AUC, sensitivity, and specificity was demonstrated, the authors discuss a myriad of confounding factors in the clinical analysis and also note the results are statistically limited. Additional clinical studies are warranted to firmly support the findings of this study that a mobile, machine learning process can be a reliable method for detection of autism outside of clinical settings.

Abbas and associates (2020) evaluated a multi-modular, machine learning-based assessment of autism via a mobile app in a blinded, multi-site clinical study comprised of 375 children who were 18 to 72 months of age. The machine learning-based assessment of autism consisted of three complimentary modules for a unified outcome of diagnostic-grade reliability. The complimentary modules (i.e., Cognoa assessment modules) included a 4-minute, parent-report questionnaire presented via a mobile app, a list of key behaviors identified from 2-minute, semi-structured home videos of children, and a 2-minute questionnaire presented to the clinician at the time of clinical assessment. The results demonstrated that the machine learning-based assessment outperformed baseline autism screening assessments (i.e., the Child Behavior Checklist [CBCL], the Modified Checklist for Autism in Toddlers, Revised [M-CHAT-R], and the Social Responsiveness Scale – Second Edition [SRS]) administered to children by 0.35 (90% Confidence Interval [CI]: 0.58 to 0.81) in specificity when operating at 90% sensitivity. Additionally, in

children less than 48 months of age, the investigators' machine learning-based assessment outperformed the most accurate baseline screening assessment by 0.18 (90% CI: 0.08 to 0.29 at 90%) in AUC and 0.30 (90% CI: 0.11 to 0.50) in specificity when operating at 90% sensitivity. The investigators discuss the limitations of the study, including that the children preselected have a high risk of autism, and that there is a need to validate this new machine learning-based assessment in the primary care clinic setting.

d-Nav

Hygieia (Livonia, MI) developed the d-Nav system, which is indicated in type 2 diabetic patients who inject insulin to manage their diabetes by calculating the next dose of insulin to aid in optimization of insulin management. The d-Nav system combines a mobile app with artificial intelligence (AI) technology that enables independent adjustments made to a patient's insulin prescription based on their historical and current glucose levels. Specifically, the d-Nav device consists of an unique FDA-cleared software that increases insulin doses when glucose patterns exceed the target and decreases insulin doses when glucose patterns fall under the target. Furthermore, the d-Nav system is accompanied with unlimited clinical support in the form of d-Nav Care Specialists who monitor individual patient data sent to the cloud to assist with proper patient use and address clinical concerns via in person and telephone communication. The d-Nav system requires a prescription from a qualified healthcare provided and is designed to enable users to significantly improve their hemoglobin A_{1c} along with a reduction in the frequency of hypoglycemia when used with outpatient therapy (Digital Therapeutics Alliance, 2021c; Hygieia, 2021).

Bergenstal and colleagues (2019) evaluated whether the combination of the d-Nav device and healthcare provider support is superior to healthcare provider support alone in a multi-center, randomized controlled study. The study consisted of 181 participants with the following inclusion criteria: 21 to 70 years of age, type 2 diabetes with a glycated hemoglobin (HbA_{1c}) concentration of 7.5% or higher (≥ 58 mmol/mol) and 11% or lower (≤ 97 mmol/mol) and on the same insulin regimen for the previous 3 months. Participants were randomly assigned to the intervention (n=93) and control (n=88) groups. The primary outcome was the comparison of

average change in HbA_{1c} from baseline to 6 months. Participant safety was determined by the frequency of hypoglycemic events. The baseline mean HbA_{1c} was 8.7% (SD 0.8; 72 mmol/mol [SD 8.8] in the intervention group and 8.55% (SD 0.8; 69 mmol/mol [SD 8.8]) in the control group. The mean decrease in HbA_{1c} from baseline to 6 months was 1.0% (SD 1.0; 11 mmol/mol [SD 11]) in the intervention group, and 0.3% (SD 0.9; 3.3 mmol/mol [SD 9.9]) in the control group ($p<0.0001$). The frequency of hypoglycemic events per month was similar between the groups (0.29 events per month [SD 0.48] in the intervention group and 0.29 [SD 1.12] in the control group; $p=0.96$). The investigators concluded that automated insulin titration guidance in combination with healthcare provider support provides superior glycemic control compared with stand-alone healthcare provider support. However, there is additional need to perform an evaluation across large healthcare systems to validate these findings.

EndeavorRx

Akili Interactive Labs, Inc. (Boston, MA) developed EndeavorRx which is an FDA-authorized digital therapeutic indicated to improve attention function as measured by computer-based testing in children ages 8 to12 years old with primarily inattentive or combined-type ADHD, who have a demonstrated attention issue. This digital treatment is delivered through an action video game experience and is designed to challenge a child's attention span during gameplay with the necessary focus and flexibility to perform multiple tasks at the same moment. EndeavorRx should be considered for use as part of a therapeutic program that may consist of clinician-directed therapy, medication, and/or educational programs, which target symptoms of the disorder. Specifically, EndeavorRx is a prescription only medical device where one prescription will provide 3 months of access to this treatment. The duration of EndeavorRx daily treatments last approximately 25 minutes and should be completed by the patient without interruption (Akili Interactive Labs, 2021; Digital Therapeutics Alliance, 2021d).

In the Software Treatment for Actively Reducing Severity of ADHD (STARS-ADHD) study, Kollins and colleagues (2020) evaluated an investigational digital therapeutic, AKL-T01, for improved attentional performance in pediatric patients with attention-deficit hyperactivity disorder (ADHD). AKL-T01 (Akili Interactive Labs, Boston, MA) targets

attention and cognitive control delivered through a video game-like interface through at-home play for 25 minutes per day, 5 days per week for 4 weeks. The STARS-ADHD study consisted of a randomized, double blind, parallel group, controlled trial of 348 pediatric patients aged 8 to 12 years with confirmed ADHD and Test of Variables of Attention (TOVA) Attention Performance Index (API) scores of -1.8 and below performed by 20 research institutions in the USA. Study participants were randomly assigned 1:1 to AKL-T01 or a digital control intervention which was in the form of a challenging and engaging word game. The study's primary outcome was a mean change in TOVA API from pre-intervention to post-intervention. Additionally, participant safety, tolerability, and compliance were also evaluated. Study participants who received AKL-T01 (n=180 [52%]; mean [SD] age, 9.7 [1.3] years) or control (n=168 [48%]; mean [SD] age, 9.6 [1.3] years), the non-parametric estimate of the population median change from baseline TOVA API was 0.88 (95% Confidence Interval [CI] 0.24-1.49; p=0.0060). The mean SD change from baseline on the TOVA API was 0.93 (3.15) in the AKL-T01 group and 0.03 (3.16) in the control group. No serious adverse events or discontinuation occurred. Participant compliance was a mean of 83 (83%) of 100 expected sessions played (SD, 29.2 sessions). The investigators concluded based on the evidence, AKL-T01 might be used to improve objectively measured inattention in pediatric patients with ADHD with minimal adverse events.

Freespira

Freespira, Inc. (Kirkland, WA) developed Freespira which is an FDA-cleared digital therapeutic that utilizes a proprietary sensor, physiologic feedback display, and coaching to instruct patients over 28-days to normalize the respiratory irregularities underlying a key physiological mediator of anxiety attacks and post-traumatic stress disorder (PTSD) symptoms (carbon dioxide hypersensitivity). Freespira is an adjunctive digital treatment for symptoms of panic disorder (PD) and PTSD used under the supervision of a healthcare professional, in combination with other pharmacological and/or non-pharmacological interventions. Specifically, Freespira consists of a small, portable case with a commercial-grade portable sensor that is capable of measuring real-time carbon dioxide (CO_2) and respiratory rate with wireless connectivity to a tablet computer that comes with a pre-installed app to guide treatment.

Training is provided from a clinically supervising coach via telehealth in the form of guidance and support on appropriate use and best practices over the 28 day duration. The functionality of Freespira is based on breath sample delivery via a nasal canula connected to the Freespira sensor and by teaching patients to breath in synch and at different rates with rising and falling audio tones. Additionally, visual graphs of respiratory rate and exhaled CO_2serve as a prompt to adjust breathing volume in order to achieve normal CO_2targets. The coach is able to see the patient's uploaded physiologic data from the app and provide patient-tailored and specific coaching to further augment engagement, adherence, and symptom reductions over time. Freespira is used for 17 minutes twice daily for 28 days at home and although a prescription is not required from a physician, this digital therapeutic must be authorized by a licensed healthcare provider (Digital Therapeutics Alliance, 2021e).

Tolin and colleagues (2017) evaluated Freespira (Palo Alto Health Sciences, Inc., Danville, CA) in a multicenter, single arm trial consisting of 69 adult participants with panic disorder (PD). Study participants received 4 weeks capnometry guided respiratory intervention (CGRI) using Freespira, which provided feedback of end-tidal CO_2($PETCO_2$) and respiration rate (RR) transmitted by a sensor device. The intervention was delivered via home use after initial training by a clinician and provided remote monitoring of participant adherence and progress by the clinician. Outcomes assessment occurred post-treatment at 2- and 12-month follow-up. CGRI was associated with a response rate of 83% and remission rate of 54%. Additionally, large decreases in panic severity were noted as well as similar decreases in functional impairment and in global illness severity. The investigators noted that gains were largely sustained at follow-up and $PETCO_2$moved from the slightly hypocapnic range to the normocapnic range. This study served as a benchmarking analyses against a prior published controlled trial and confirmed prior clinical results and further supported the viability of CGRI in the treatment of PD.

Halo AF Detection System

LIVMOR, Inc. (Frisco, TX) developed the Halo AF Detection System which is an FDA-cleared digital technology that is delivered on a Samsung wearable smartwatch device and provides continuous

monitoring of pulse rhythms for the detection of atrial fibrillation (AF), on demand during the day and automatically overnight. A prescription is required from a physician for patients to use the Halo AF Detection System (LIVMOR, 2020).

Currently, there is a lack of published peer-reviewed evidence available.

Insulia

Voluntis (Cambridge, MA) developed the Insulia app which is an FDA-cleared software medical device that is indicated for use by healthcare professionals (HCPs) and their type 2 adult diabetes patients who are receiving treatment with a long-acting insulin analog. Insulia facilitates insulin titration for patients using any brand of basal insulin including Lantus, Levemr, Toujeo, Tresiba, and Basaglar. This app is complimentary to basal insulin therapy and may be used on a compatible smartphone or computer. The Insulia app's functionality includes the secure capture, storage, and transmission of the patient's diabetes related data via a web portal. Additionally, the visual reports and graphs supported by this app enables the HCP to review, analyze, and evaluate patient data to better manage the patient's diabetes. The app also comes with an accompanying coaching feature to ensure continual patient support. A prescription is required from a qualified healthcare provider for the patient to use the Insulia app (Digital Therapeutics Alliance, 2021f; Voluntis, 2021).

In the TeleDiab-2 study, Franc and colleagues (2019) evaluated the efficacy and safety of two telemonitoring systems to optimize basal insulin (BI) in participants with inadequately controlled type 2 diabetes. The study was a 13-month randomized controlled trial consisting of 191 individuals (mean age 58.7 years, mean hemoglobin A_{1c} [HbA_{1c}] 8.9%). Study participants were randomized into three groups including group 1 (standard care, n=63), group 2 (interactive voice response system, n=64), and group 3 (Diabeo-BI app software, n=64). At 4 months follow-up, HbA_{1c} reduction was significantly higher in the telemonitoring groups (group 2: -1.44% and group 3: -1.48% vs group 1: -0.92%; $p< 0.002$). Furthermore, target fasting blood glucose was achieved by twice as many patients in the telemonitoring groups as in the control group, and insulin doses were also titrated to greater levels. The absence of severe

hypoglycemia was noted in the telemonitoring groups. Mild hypoglycemia frequency was similar in all groups. The investigators concluded both telemonitoring systems improved glycemic control to a similar extent without an increase in hypoglycemic episodes.

leva Pelvic Health System

Renovia Inc. (Boston, MA) developed the leva Pelvic Health System which is an FDA-cleared medical device and consists of an intravaginal wand with motion sensors and app-based software program. This medical device is indicated for urinary incontinence in women with the aim of strengthening pelvic floor muscles and rehabilitating and training weak pelvic floor muscles in order to manage stress, mixed and mild to moderate urgency urinary incontinence, including overactive bladder. Under the guidance of the leva app, the patient performs 2 and a half minute exercise sessions twice a day for 8 to 12 weeks or until patient satisfaction with results. The patient performs the exercise while standing with the leva wand placed intravaginally for the exercise duration followed by immediate removal after use. Exercise data is transmitted from the wand to the software program on the patient's smartphone and the healthcare provider receives a monthly summary and individual patient reports. This securely captured and transmitted data highlights therapy adherence, symptoms, perceived improvement, and material remarks from leva's care management team which can then be used for short- and long-term follow up care. The leva Pelvic Health System requires a prescription from a qualified healthcare provider for patients to use this medical device as first-line therapy either alone or in combination with other therapies (Digital Therapeutics Alliance, 2021g; Renovia, 2021).

Rosenblatt and colleagues (2019) evaluated the effectiveness and patient satisfaction of the leva Pelvic Digital Health System (leva), a pelvic floor muscle training (PFMT) with an accelerometer-based system for the treatment of female urinary incontinence (UI). This prospective, single-center, open label study consisted of 23 female participants who were premenopausal with mild to moderate stress or mixed UI for 6 weeks duration with supervision. The study results were as follows: the Urogenital Distress Inventory (UDI) score decreased from 36.7 ± 4.7 to 1.45 ± 0.8 at 6 weeks ($p<0.0001$), the Patient's Global Impression of Severity score decreased from 1.5 ± 0.1 to 0.2 ± 0.1 ($p<0.0001$) at study

endpoint, the pelvic floor muscle (PFM) contraction duration increased from 13 ± 2.6 at baseline to 187 ± 9.6 seconds (p<0.0001), repeated contractions in 15 seconds increased from 5.9 ± 0.4 at enrollment to 9.6 ± 0.5 at 6 weeks (p< 0.0001), and maximum pelvic floor angle (a measure of lift) increased from 65.1 ± 2.0˚ to 81.1 ± 1.8˚ (p<0.0001). Additionally, increasing PFM contraction duration and maximum pelvic floor angle correlated with decreasing UDI-6 scores, r = -0.87, p=0.01; r = -0.97, p=0.0003, respectively. Device-related adverse events were absent.

Weinstein and colleagues (2021) evaluated whether the use of an intravaginal motion-based digital therapeutic device for pelvic floor muscle training (PFMT) was superior to PFMT alone in women with stress-predominant urinary incontinence (SUI). This study was a multicenter, randomized-controlled trial consisting of 61 female participants with SUI or SUI-predominant mixed urinary incontinence. The intervention group (n=29) was treated with PFMT using the device and the control group (n=32) received treatment with PFMT alone. Primary outcomes were measured at 8 weeks and included change in Urinary Distress Inventory, short-version and improvement in the Patient Global Impression of Improvement. In addition, participants completed Pelvic Organ Prolapse and Colorectal-anal Distress Inventories, Pelvic-Floor-Impact Questionnaire and a 3-day bladder diary. Study results were as follows: no statistical difference was noted in Urinary Distress Inventory, short-version scores between the intervention (-13.7 ± 18.7) and the control group (-8.7 ± 21.8; p=0.85), or in Patient Global Impression of Improvement (interventions 51.7% and control group 40.6%; p=0.47). Furthermore, Pelvic Organ Prolapse and Colorectal-anal Distress Inventories and Pelvic-Floor-Impact Questionnaire scores improved significantly more in the intervention group than the control group (all p<0.05) and median number of SUI episodes decreased from baseline to 8 weeks by -1.7 per day [(-3)-0] in the intervention group and -0.7[(-1)-0] in the control group, (p=0.047). Notably, this study was prematurely stopped due to device technical considerations.

Nerivio

Theranica Bio-Electronics Ltd. (Montclair, NJ) developed Nerivio which is a wireless wearable neuromodulation device that is operated by a smartphone software application. Nerivio device is FDA-cleared via the

De Novo Pathway and is indicated for the acute treatment of migraine with or without aura in patients 12 years of age or older. Nerivio can serve as a replacement for current migraine therapy or work in combination with existing therapy. The functionality of the Nerivio device is based on it being applied to the patient's upper arm at the onset of migraine with self-administered treatment that is adjusted at an intensity that is not painful for a duration of 45 minutes. Notably, patients with congestive heart failure, severe cardiac disease, cerebrovascular disease, or uncontrolled epilepsy are not candidates for Nerivio treatment. Additionally, patients with active implantable medical devices, such as a pacemaker or hearing aid implant, should not use Nerivio. A prescription from a qualified healthcare provider is required for patients to use Nerivio (Digital Therapeutics Alliance, 2021h).

Grosberg and colleagues (2021) evaluated the efficacy and safety of remote electrical neuromodulation (REN) in patients with chronic migraine. This was an open-label, single-arm study consisting of 91 participants with chronic migraine and whose headaches were treated with the REN device (Nerivio, Theranica Bio-Electronics Ltd, Israel) for 4 weeks. In addition, participants used an electronic diary to record their symptoms at treatment initiation, 2 hours after treatment, and 24 hours after treatment. The primary outcome was the percentage of participants who achieved pain relief at 2 hours post-treatment. Secondary outcomes included pain freedom and improvement of associated symptoms and functional disability. Study results were as follows: pain relief and pain disappearance at 2 hours were achieved by 59.3% (54/91) and 20.9% (19/91) of participants, respectively, and sustained pain relief at 24 hours was observed in 64.4% (29/45) of those who achieved pain relief at 2 hours. REN had a favorable effect on nausea, photophobia, and phonophobia and improved functional ability. A device-related adverse event was observed.

Hershey and colleagues (2021) conducted a post-hoc analysis from a clinical study consisting of 35 adolescent participants which compared the efficacy of remote electrical neuromodulation (REN) to that of standard-care medications (triptans or over-the-counter medications) for the acute treatment of migraine. Specifically, efficacy was compared between a run-in phase in which attacks were treated with standard-care medications, and an intervention phase in which attacks were treated with REN.

Efficacy was compared using the McNemar's test at four endpoints (two hours post-treatment); single-treatment pain freedom and pain relief, and consistency of pain freedom and pain relief (defined as response in at least 50% of the available first four treatments). Post-hoc analysis results were noted as follows: at two hours post-treatment, pain freedom was achieved by 37.1% of participants with REN, vs. 8.6% of participants with medications (p=0.004), pain relief was achieved by 71.4% with REN, vs. 57.1% with medications (p=0.225), consistency of pain freedom was achieved by 40% with REN, vs.8.6% with medications (p<0.001), and consistency of pain relief was achieved by 80.0% with REN, vs. 57.2% with medications (p=0.033). The investigators concluded that REN may have a higher efficacy than certain standard-care medications for the acute treatment of migraine in adolescents.

NightWare

NightWare, Inc. (Hopkins, MN) developed NightWare which is an FDA-cleared medical device with a Breakthrough Device designation and is indicated for the reduction of sleep disturbance associated with nightmares in adult patients 22 years of age or older who suffer from nightmare disorder or have nightmares from post-traumatic stress disorder (PTSD). The functionality of this medical device is based on artificial intelligence (AI) and smart technology on the Apple Watch. NightWare is driven by the Apple Watch heart rate monitor sensor and other biometric sensors to continually evaluate the patient's level of sleep disturbance (i.e., stress index) during sleep by tracking heart rate and body movements to determine nightmare occurrence. Once a nightmare is detected, the NightWare system quickly sends vibrations to interrupt nightmares without waking the patient. Through AI algorithms, both intensity and frequency of vibrations are based on an individual's specific needs at that moment. As the NightWare system captures more data, it adapts to the patient's sleep patterns. A prescription from a physician is required for NightWare to be used by patients (NightWare, 2021).

Currently, there is a lack of published peer-reviewed evidence available.

reSET

Pear Therapeutics, Inc. (Boston, MA) developed reSET which is an FDA-cleared software application that provides cognitive behavioral therapy for substance abuse disorder as an adjunct to a contingency management system for patients 18 years of age and older who are enrolled in outpatient treatment under the supervision of a healthcare provider. Specifically, reSET delivers therapy established on the community reinforcement approach (CRA), an intensive form of validated neurobehavioral therapy for substance abuse disorder in addition to contingency management and reinforcement of concept mastery to augment learning. reSET consists of 62 interactive modules (32 core modules and 30 supplemental modules). The core modules involve CRA concepts, skill building to reinforce behavior change and prevent relapse. The supplemental modules focus on specific topics (e.g., relationship skills, living with hepatitis C). Modules may typically take 10 to 20 minutes to complete. The reSET app is supported on a mobile operating system (e.g., smartphone or tablet). A prescription is required from a licensed healthcare provider for a patient to use reSET which provides a 12 week duration of therapy (Digital Therapeutic Alliance, 2021i; Pear Therapeutics, 2021a).

Campbell and colleagues (2014) evaluated the effectiveness of the Therapeutic Education System (TES), an internet-delivered behavioral intervention inclusive of motivational incentives, as a clinician-extender in the treatment of substance abuse disorder. The multisite randomized controlled trial consisted of adult men and women (n=507) entering 10 outpatient addiction treatment programs who were randomly assigned to receive 12 weeks of either treatment as usual (n=252) or treatment as usual plus TES, with the intervention replacing about 2 hours of standard care per week (n=255). TES involved 62 computerized interactive modules covering skills for achieving and maintaining abstinence, plus prize-based motivational incentives contingent on abstinence and treatment adherence. Treatment as usual involved individual and group counseling at the participating programs. The primary endpoint measures were abstinence from drugs and heavy drinking (measured by twice-weekly urine drug screens and self-report) and time to dropout from treatment. The study results were as follows: participants in the TES group had a lower dropout rate (hazard ratio=0.72, 95% Confidence Interval [CI] = 0.57, 0.92) and a greater abstinence rate (odds ratio=1.62, 95% CI=1.12, 2.35). This effect was more dramatic among participants

who had a positive urine drug or breath alcohol screen at study entry (n=228) (odds ratio=2.18, 95% CI=1.3, 3.68). The investigators noted that additional investigation is needed to assess effectiveness in non-specialty clinical settings and to distinguish the effects of the community reinforcement approach and contingency management facets of TES.

reSET-O

Pear Therapeutics, Inc. (Boston, MA) developed reSET-O which is an FDA-cleared software application that provides cognitive behavioral therapy for opioid use disorder as an adjunct to outpatient treatment that includes transmucosal buprenorphine and contingency management outpatient treatment for patients 18 years of age or older who are under the supervision of a healthcare provider. Specifically, reSET-O delivers behavioral therapy based on the community reinforcement approach (CRA), a type of cognitive therapy targeting opioid use disorder. In addition, reSET-O combines CRA with reinforcement of concept mastery which should be initiated concurrently with contingency management and buprenorphine treatment to aid patient retention with opioid use disorder in outpatient treatment. reSET-O is supported on a mobile operating system (e.g., smartphone or tablet) and is a 12-week software application that requires a prescription from a licensed healthcare provider for patient use (Digital Therapeutics Alliance, 2021j; Pear Therapeutics, 2021a).

Christensen and colleagues (2014) examined the benefit of adding an internet-delivered behavior therapy to a buprenorphine medication program and voucher-based motivational incentives. This was a block-randomized, unblinded, parallel, 12-week treatment study consisting of 170 opioid-dependent adult participants (mean age = 34.3 years; 54.1% male; 95.3% white). Study participants received either an internet-based community reinforcement approach intervention plus contingency management (CRA+) and buprenorphine or contingency management alone (CM-alone) plus buprenorphine. The primary endpoints, measured over the course of treatment, were longest continuous abstinence, total abstinence, and days retained in treatment. Study results were as follows: in comparison to CM-alone participants, CRA+ participants displayed, on average, 9.7 total days more of abstinence (95% confidence interval [CI=2.3, 17.2]), and had a reduced hazard of dropping out of treatment (hazard ratio=0.47; 95% CI [0.26, 0.85]). Previous treatment for opioid

dependence significantly mediated the additional improvement of CRA+ for longest continuous days of abstinence. The investigators concluded that an internet-based CRA+ treatment has efficacy and adds clinical benefits to a contingency management/medication based program for opioid dependence.

Maracich and colleagues (2021) evaluated the safety and efficacy of a digital therapeutic in treatment-seeking individuals with opioid use disorder (OUD) in an analysis of randomized clinical data (RCT) data. This secondary analysis of a RCT consisted of 170 adult participants meeting DSM-IV criteria for OUD. Participant randomization to 12 weeks of treatment-as-usual (TAU) or TAU plus a digital therapeutic occurred. TAU consisted of buprenorphine maintenance therapy, 30 min biweekly clinician interaction, and abstinence-based contingency management. The digital therapeutic consisted of 67 digital, interactive educational modules based on the Community Reinforcement Approach. The primary outcomes were treatment retention and abstinence (negative urine drug screen) during weeks 9-12 of treatment. Adverse events monitoring served as the safety parameter. The study results were as follows: recipients of TAU plus a digital therapeutic had significantly greater odds of opioid abstinence during weeks 9-12 compared to TAU: 77.3% vs. 62.1%, respectively (p=0.02), or 2.08, 95% confidence interval [CI] 1.10-3.95, and the risk of participants leaving treatment was significantly lower in the digital therapeutic group (hazard ratio [HR] 0.49, 95% CI 0.26-0.92). The difference in observed rate of adverse events between groups was not significant (p=0.42). The investigators concluded that TAU plus a digital therapeutic improves clinically significant patient outcomes including abstinence from illicit opioids and retention in treatment compared with TAU.

Somryst

Pear Therapeutics, Inc. (Boston, MA) developed Somryst which is an FDA-cleared software app that provides digital cognitive behavioral therapy for insomnia (CBT-I) for chronic insomnia in patients who are 22 years of age and older. With the aim of improving a patient's insomnia symptoms, Somryst is accessible on a mobile device (e.g., smartphone or tablet) and consists of 6 treatment cores focused on CBT-I concepts (e.g., sleep restriction and consolidation, stimulus control and cognitive

restructuring). Patients should complete one core every 7 days and complete their daily sleep diary and follow the sleep restriction window recommendation provided by this software app. Somryst uses sleep restriction and consolidation and, therefore, is not to be used in individuals with any disorder worsened by sleep restriction (e.g., bipolar disorder, schizophrenia, other psychotic spectrum disorders), untreated obstructive sleep apnea, parasomnias, epilepsy, high risk of falls, pregnancy, and unstable or degenerative illness considered to be exacerbated by sleep restriction delivered as a part of CBT-I. Somryst is a 9-week therapy duration that is complimentary to current therapy. Additionally, a prescription from a licensed healthcare provider is required for a patient to use this software app (Digital Therapeutics Alliance, 2021k; Pear Therapeutics, 2021b).

Christensen and colleagues (2016) evaluated whether an online self-help insomnia program could reduce depression symptoms. This was a randomized controlled study consisted of 1149 participants (aged 18-64 years) with insomnia and depression symptoms, but who did not meet criteria for major depressive disorder. Study participants were randomly assigned (1:1) to receive SHUTi (a 6 week, modular online insomnia program based on cognitive behavioral therapy for insomnia) or HealthWatch (an interactive, attention-matched, internet-based placebo control program). The primary endpoint was depression symptoms at 6 months, as measured with the Patient Health Questionnaire (PHQ-9). Results were based on 581 (51%) participants completing the study program assessments at 6 weeks and 504 (44%) participants completing 6 months follow up. SHUTi recipients had significantly lower depression symptoms on the PHQ-9 at 6 weeks and 6 months compared with HealthWatch ($F[\text{degrees of freedom } 2,640.1] = 37.2$, $p<0.0001$). Major depressive disorder was diagnosed in 22 (4%) participants at 6 months (n=9 in the SHUTi group and n=13 in the HealthWatch group), with no superior effect of SHUTi vs. HealthWatch (Fisher’s exact test=0.52; p=0.32). No adverse events were noted. The investigators concluded that online cognitive behavior therapy for insomnia treatment is a pragmatic and effective method to reduce depression symptoms and may have the capability to reduce depression at the population level.

Ritterband and colleagues (2017) evaluated a web-based, automated cognitive behavior therapy for insomnia (CBT-I) to improve insomnia in 9 weeks (short-term) and 1 year (long-term). This was a randomized clinical study consisting of 303 participants with chronic insomnia. Participant randomization occurred 1:1 where participants either received the internet CBT-I (Sleep Healthy Using the Internet [SHUTi]) or the online patient education program. SHUTi was a 6-week fully automated, interactive, and tailored web-based program incorporating the primary tenets of face-to-face CBT-I, whereas the online patient education program consisted of nontailored and fixed online information about insomnia. The primary sleep outcomes consisted of self-reporting online ratings of insomnia severity (Insomnia Severity Index) and online sleep diary-based values for sleep-onset latency and wake after sleep onset, collected prospectively for 10 days at each assessment period. The secondary sleep outcomes were comprised by sleep efficiency, number of awakenings, sleep quality, and total sleep time. The results of the three primary sleep outcomes revealed that the overall group x time interaction was significant for all variables, favoring SHUTi recipients (Insomnia Severity Index [F3, 1063 = 20.65, p<0.001), sleep-onset latency [F3, 1042 = 12. 68, p<0.001]). With-in group effect sizes exhibited improvements from baseline to post-assessment for the SHUTi recipients (range, Cohen d=0.79 [95% confidence interval [CI], 0.55-1.04] to d=1.90 [95% CI, 1.62-2.18]). Treatment effects were sustained at the 1 -year follow-up (SHUTi Insomnia Severity Index d=2.32 [95% CI, 2.01-2.63], sleep-onset latency d=1.41 [95% CI, 1.15-1.68], and wake after sleep onset d=0.95 [95% CI, 0.70-1.21]), with 56.6% (69 of 122) reaching remission status and 69.7% (85 of 122) deemed treatment responders at 1 year based on Insomnia Severity Index data. Secondary sleep outcomes, with the exception of total sleep time, showed significant overall group x time interactions, favoring the SHUTi group. The investigators concluded that internet-delivered CBT-I may have a pivotal role in the communication of effective behavioral treatments.

CPT Codes / HCPCS Codes / ICD-10 Codes

Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by "+":

Code	Code Description
Code	Code Description
HCPCS codes not covered for indications listed in the CPB:	
Prescription digital therapeutics - no specific code	
Other HCPCS codes related to the CPB:	
T1505	Electronic medication compliance management device, includes all components and accessories, not otherwise classified

The above policy is based on the following references:

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