Regence

Medical Policy Manual Medicine, Policy No. 175.05

Digital Therapeutic Products for Post-traumatic Stress Disorder and Panic Disorder

Effective: February 1, 2025

Next Review: December 2025
Last Review: December 2024

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 established treatments for post-traumatic stress disorder and panic disorder.

MEDICAL POLICY CRITERIA

Notes:

- Member contracts for covered services vary. Member contract language takes precedence over medical policy.
- This policy addresses the use of practitioner-prescribed software applications for therapeutic intervention.
- 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).

I. The use of a digital therapeutic product for the treatment of panic disorder and/or post-traumatic stress disorder, including but not limited to Freespira®, either as a stand-alone treatment or as an adjunct to standard treatment, is considered **investigational**.

II. The use of a digital therapeutic product for the treatment of nightmare disorder or nightmares from post-traumatic stress disorder, including but not limited to NightWare™, either as a stand-alone treatment or as an adjunct to standard treatment, is considered **investigational.**

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

PANIC DISORDER

Panic disorder is defined by recurrent, untriggered panic attacks with one month or more of worry about future attacks or a maladaptive change in behavior related to the attacks.[1] Although other symptoms such as headache, tinnitus, and uncontrollable crying are common, they do not define panic attacks. The most common symptom of a panic attack is heart palpitations. Panic disorder evaluation should be considered in patients who express recurrent, pervasive worry or present with somatic symptoms not attributed to underlying medical conditions. The Patient Health Questionnaire for Panic Disorder (PHQ-PD) is used to screen for panic disorder.

Treatment

Initial therapies for panic disorder include cognitive behavioral therapy and anti-depressants, including selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors.[1] Benzodiazepines are not recommended for first-line treatment or long-term use due to adverse reactions, risk of dependence, and higher mortality. No consistent evidence currently supports a specific prevention strategy for panic disorder, but exercise may be beneficial. Despite limited evidence, beta blockers are frequently used to treat acute symptoms of panic attacks. The effectiveness of buspirone for panic disorder is uncertain. Antipsychotics or sedating antihistamines are not recommended for panic disorder due to limited evidence of effectiveness and adverse effects.

POST-TRAUMATIC STRESS DISORDER (PTSD)

The *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision (DSM-5-TR)* defines a traumatic event as an event, or series of events, in which an individual has

been personally or indirectly exposed to actual or threatened death, serious injury, or sexual violence.[2] There is a wide spectrum of psychological responses to traumatic events, including transient, non-debilitating symptoms; transient, acute stress response; acute, time-limited, and clinically significant acute stress disorder; and symptoms that persist beyond one month (PTSD) that might become chronic, if untreated. PTSD symptoms include intrusive thoughts, nightmares and flashbacks of past traumatic events, avoidance of reminders of trauma, hypervigilance, and sleep disturbance, all of which lead to considerable social, occupational, and interpersonal dysfunction.

Diagnosis of PTSD is challenging due to heterogeneous symptoms and patient resistance to discuss past trauma.[3] Comprehensive psychological assessment is used for PTSD screening. Example screening assessments include the PTSD checklist (PCL-5), a 20-item self-report measure used to screen patients for PTSD and monitor the severity of symptoms over time and the Clinician Administered PTSD Scale (CAPS), a 30-item, structured interview used to diagnose PTSD in the past week, past month, or lifetime, and to assess the severity of PTSD symptoms. DSM-5 criteria are used to diagnose PTSD.

Treatment

A 2023 systematic review conducted by The Department of Veteran's Affairs and Department of Defense reported that psychotherapy and pharmacotherapy are effective at treating PTSD.[2] Clinical guidelines based on this evidence review recommend trauma-focused psychotherapy over pharmacotherapy if both treatment types are available and feasible. The following individual, manualized, or trauma-focused psychotherapies are recommended for the treatment of PTSD: Cognitive Processing Therapy, Eye Movement Desensitization and Reprocessing, Prolonged Exposure, Ehlers' Cognitive Therapy for PTSD, Present-Centered Therapy, or Written Exposure Therapy. Regarding pharmacotherapy, selective serotonin reuptake inhibitors (SSRI) or serotonin norepinephrine reuptake inhibitors (SNRI) (e.g., paroxetine, sertraline, or venlafaxine) are recommended for the treatment of PTSD.

The following approaches are currently used to treat PTSD-associated nightmares: medications; image rehearsal therapy; cognitive behavioral therapy; cognitive behavioral therapy for insomnia; eye movement desensitization and reprocessing; exposure, relaxation, and rescripting therapy.[4] Current treatments for nightmare disorder include image rehearsal therapy, cognitive behavioral therapy, exposure, relaxation, and rescripting therapy, hypnosis, lucid dreaming therapy, progressive deep muscle relaxation, sleep dynamic therapy, self-exposure therapy, systematic desensitization, and the testimony method.

REGULATORY STATUS

The Freespira® Canary Breathing System (Freespira, previously PaloAlto Health Sciences) received United States (US) Food and Drug Administration (FDA) 510(k) premarket clearance on July 23, 2018 and was previously approved as the Canary Breathing™ System in 2013 (K131586, K180173).[5, 6] Freespira capnometry-assisted respiratory therapy is intended for use as a relaxation treatment for the reduction of stress by leading the user through guided and monitored breathing exercises. The device is indicated as an adjunctive treatment of symptoms associated with panic disorder and/or PTSD, to be used under the direction of a healthcare professional, together with other pharmacological and/or non-pharmacological interventions. It is a small breathing sensor with a tablet that is used twice a day for 17 minutes. Individuals are trained to use the sensor with the mobile application to measure and

display their end-tidal carbon dioxide ($EtCO_2$) level, respiratory rate, and the effects of different breathing habits on $EtCO_2$. Product code: HCC, CCK.

The NightWare™ Kit (NightWare, Inc.) received US FDA breakthrough device designation on May 27, 2023 (DEN200033).[7] The NightWare™ digital therapeutic provides vibrotactile feedback on an AppleWatch® based on an analysis of heart rate and motion during sleep. NightWare™ is indicated for the temporary reduction of sleep disturbance related to nightmares in adults 22 years or older who suffer from nightmare disorder or have nightmares from PTSD. It is intended for home use. The NightWare™ therapeutic platform uses a proprietary AppleWatch® and Apple iPhone application. The application learns the wearer's sleep patterns and customizes treatment to the individual. The application monitors the wearer's heart rate and movement during sleep and provides a vibration alert when a stress threshold is reached, intended to interrupt the nightmare but not awaken the patient. Users wear the watch only while sleeping and not during the day. Product code: QMZ.

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 THERAPIES FOR PANIC DISORDER AND PTSD

Clinical Context and Therapy Purpose

Panic disorder is an anxiety disorder associated with marked impairment in social and occupational functioning, significant impact on quality of life, and high utilization of health care services.[8] Fearful interpretation of bodily symptoms such as tachycardia, shortness of breath, chest tightness, and dizziness with catastrophic beliefs is the core of the diagnosis and differentiates it from other anxiety disorders. Many individuals with panic disorder hyperventilate, and it has been suggested that respiratory abnormality associated with panic disorder may be due to a hypersensitivity to carbon dioxide (CO_2). Based on the recognition of subtle respiratory irregularities associated with hyperventilation in individuals with panic disorder and CO_2 sensitivity, Meuret (2008) developed a breathing intervention focused on normalizing both $EtCO_2$ levels and respiratory rate.[9] The protocol provided breath-to-breath

feedback of $EtCO_2$, while modeling paced breathing at four different respiratory rates. Administered as twice daily 17-minute sessions over a four-week period, the authors reported that 86% of participants reported zero weekly panic attacks. This improvement was durable over time, as 73% of participants reported zero weekly attacks one-year post-treatment.

PTSD is marked by symptoms of hyperarousal, difficulties with emotional regulation, negative affect, and autonomic dysfunction.[3] Carbon dioxide hypersensitivity may be responsible for mediating some PTSD symptoms as CO_2 challenge tests in individuals with established PTSD have been shown to provoke a panic attack.[10, 11] Since the characteristic of CO_2 hypersensitivity is shared by both PTSD and panic disorder, extending the use of Freespira® to a population with PTSD is a logical and potentially valuable clinical tool given the lack of medication-free treatment options for PTSD.

The purpose of prescribed therapeutic digital applications is to provide a treatment option that is an alternative to, or an improvement on existing therapies, for individuals with panic disorder and PTSD. Panic symptoms may be associated with more shallow and rapid breathing. Freespira® addresses rapid and shallow breathing that may contribute to panic symptoms through training of respiratory control.

Freespira®

Nonrandomized Studies

Ostacher (2021) assessed Freespira® in a single-center, single-arm study of 55 adults with a primary DSM-5 diagnosis of PTSD (CAPS-5 score greater than or equal to 30 and Clinical Global Impressions Scale [CGI-S] score greater than or equal to four).[12] Participants were excluded if they were using any concurrent evidenced-based therapy for PTSD or had concurrent psychotic disorder, alcohol or drug use disorder requiring acute medical treatment, epilepsy or recent seizures; or cardiovascular or pulmonary disease. Participants were treated for four weeks with twice-daily, 17-minute, at-home Capnometry Guided Respiratory Intervention (CGRI) sessions. The primary efficacy outcome was 50% of participants achieving a greater than or equal to six-point decrease in CAPS-5 score at two-month follow-up. 88% (95% Confidence Interval [CI] 74 to 96%) of participants met the primary endpoint. Mean CAPS-5 scores decreased from 49.5 [±9.2] at baseline to 27.1 [±17.8] at two months, and mean CAPS-5 scores were 26.2 (±18.4) at six-month follow-up. Respiratory rate decreased, and $EtCO_2$ levels increased. All participants completed the treatment, and 48 (87%) participants completed the post-treatment assessment. 42 (76%) participants completed two-month follow-up, and 38 (69%) of participants completed six-month follow-up. No clear description of reasons for missingness, characteristics of missing observations, or sensitivity analyses of missing data assumptions were provided. In addition to significant loss to follow-up, this study is limited by lack of a comparison group or placebo control.

Kaplan (2020) published a single-arm, payer-funded (Highmark) multi-center single-arm study of Freespira® among 52 adults with a primary diagnosis of panic disorder (“moderately ill” on the CGI-S, score greater than or equal to four). Participants were either off medications or stable on medications prior to, during, or immediately after the four-week Freespira® treatment. Participants were excluded if they were receiving other psychological treatment or had evidence of organic mental disorder, severe suicidality, psychotic disorder, substance dependence, uncontrolled cardiovascular or pulmonary disease, or seizures. Treatment was delivered in the same manner as in Ostacher (2021), and participants completed weekly check-ins with a therapist. This study investigated whether treating panic disorder with

Freespira® would reduce medical costs and improve outcomes over one year. Panic symptoms were assessed using the Panic Disorder Severity Scale (PDSS). Post-treatment, PDSS scores improved from 14.4 (±3.8) at baseline to 4.9 (±3.4). At six-month follow-up, mean PDSS was 4.1 (±4.3), and at 12-month follow-up, mean PDSS was 4.4 (±4.5).

Tolin (2017) evaluated Freespira® in a multi-site, single-arm study that enrolled 69 adults with a primary diagnosis of panic disorder.[13] Participant diagnoses were based on the Mini International Diagnostic Interview, and participants were rated as "moderately ill" or greater on the CGI-S. Participants were excluded if they were receiving other psychological treatment; unresponsive to cognitive-behavioral therapy; or had evidence of organic mental disorder, severe suicidality, psychotic disorder, substance dependence, uncontrolled cardiovascular or pulmonary disease, or seizures. Participants received four weeks of CGRI using Freespira®. The intervention was delivered in an at-home setting after initial training by a clinician and provided remote monitoring of participant adherence and progress. The primary outcome was score on the PDSS. 53 (77%) participants completed the treatment, and 48 (70%) patients completed the post-treatment assessment. 46 (67%) participants completed two-month follow-up, 42 (61%) completed six-month follow-up, and 33 (48%) completed 12-month follow-up. Mean PDSS was 14.8 (±3.6) at baseline and 5.4 (±4.4) post-treatment, with a mean change of 9.4. At two months, mean PDSS was 6.0 (±5.2), with a mean change from baseline of 8.8. At 12 months, mean PDSS was 5.0 (±6.2) with a mean change from baseline of 9.4. This study is limited by significant dropout rates of 3%, 39%, and 52% at two, six, and 12 months of follow-up, and consequently data is missing for over 30% of study participants. This study is also limited by small sample size and lack of a comparison group or placebo control.

Section Summary

The evidence for digital therapeutic products for the treatment of panic disorder and PTSD with capnometry guided respiratory intervention (Freespira®) includes multiple single-arm studies. Relevant outcomes are symptoms, functional outcomes, quality of life, and treatment-related morbidity. Several questions remain regarding the efficacy of, and adherence to, these treatments based on the limitations of the included studies. Additional high-quality randomized trials with a clear design for testing a pre-specified hypothesis, comparison to standard treatments or sham controls, and long-term follow-up and are needed to establish the effectiveness and durability of digital therapeutic products for panic disorder and PTSD.

NightWare™

Randomized Clinical Trials

Davenport (2023) published results from a double-blind, sham-controlled RCT that evaluated efficacy of the NightWare™ System among veterans with impaired sleep secondary to trauma-related nightmares.[14] The trial was designed to enroll 240 participants with PTSD and nightmares, however, only 70 were enrolled. Patients with high suicide risk; cardiovascular comorbidities; current use of varenicline, beta-blockers, non-dihydropyridines; regular Circadian rhythm disruption; sleep-related comorbidities; and active substance abuse were excluded. Data from 63 trial participants were included on the primary and secondary outcome measures. The primary outcome was the difference in the Pittsburgh Sleep Quality Index (PSQI). The change from baseline was numerically higher for the NightWare™ group compared to sham, but the difference did not achieve statistical significance. There was no statistical difference observed in multiple other secondary endpoints such as change from baseline to day 30 in the active treated arm versus sham in the following outcome measures:

PCL-5, Patient Health Questionnaire 9-item depression scale (PHQ-9), Trauma-Related Nightmare Survey (TRNS), Functional Outcomes of Sleep Questionnaire (FOSQ-10), and Veterans RAND 12 Item Health Survey (VR-12). This study is limited by unclear blinding and lack of accessor blinding, statistical power not calculated for the primary outcomes, lack of power calculations, and inadequate control for selection bias. Further, the trial failed to achieve recruitment goals and was likely underpowered.

Section Summary

For individuals with nightmare disorder or PTSD-associated nightmares who receive NightWare™, the evidence includes a single trial. Relevant outcomes are symptoms, functional outcomes, quality of life, and treatment-related morbidity. The single pivotal trial did not meet the primary efficacy endpoint and was likely underpowered. Additional high-quality randomized trials with a clear design for testing a pre-specified hypothesis, comparison to standard treatments, and long-term follow-up and are needed to establish the effectiveness and durability of digital therapeutic products for panic disorder and PTSD. Currently, there is not enough evidence to determine whether digital therapeutics improve health outcomes for panic PTSD-related nightmares.

PRACTICE GUIDELINE SUMMARY

Department of Veteran's Affairs and Department of Defense (VA/DoD)

The VA/DoD published evidence-based clinical practice guidelines for Management of Post-traumatic Stress Disorder and Acute Stress Disorder in 2023.[2]

Regarding non-pharmacological treatments for PTSD, including digital therapeutics, the guidelines state:

"There is insufficient evidence to recommend for or against the following somatic therapies for the treatment of PTSD: capnometry-assisted respiratory therapy, hyperbaric oxygen therapy, neurofeedback, NightWare™, repetitive transcranial magnetic stimulation, stellate ganglion block, or transcranial direct current stimulation."

Regarding treatments for nightmares, the guidelines state:

"There is insufficient evidence to recommend for or against the following treatments for nightmares associated with PTSD: Imagery Rehearsal Therapy, Exposure Relaxation and Rescripting Therapy, Imaging Rescripting and Reprocessing Therapy, or NightWare™."

SUMMARY

There is not enough research to show that digital therapeutic products for the treatment of post-traumatic stress disorder (PTSD), panic disorder, or nightmare disorder improve net health outcomes as much as or more than established treatments. No clinical guidelines based on research recommend digital therapeutic products for the treatment of PTSD, panic disorder, or nightmare disorder. Therefore, digital therapeutics for the treatment of PTSD, panic disorder, and nightmare disorder are considered investigational.

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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	None	

Codes	Number	Description
HCPCS	A9291	Prescription digital cognitive and/or behavioral therapy, FDA cleared, per course of treatment
	G0552	Supply of digital mental health treatment device and initial education and onboarding, per course of treatment that augments a behavioral therapy plan
	G0553	First 20 minutes of monthly treatment management services directly related to the patient's therapeutic use of the digital mental health treatment (dmht) device that augments a behavioral therapy plan, physician/other qualified health care professional time reviewing information related to the use of the dmht device, including patient observations and patient specific inputs in a calendar month and requiring at least one interactive communication with the patient/caregiver during the calendar month
	G0554	Each additional 20 minutes of monthly treatment management services directly related to the patient's therapeutic use of the digital mental health treatment (dmht) device that augments a behavioral therapy plan, physician/other qualified health care professional time reviewing data generated from the dmht device from patient observations and patient specific inputs in a calendar month and requiring at least one interactive communication with the patient/caregiver during the calendar month

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