Freespira for Panic Disorder and Posttraumatic Stress Disorder

Health Technology Assessment

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Executive Summary

Background

Freespira is a digital therapeutic indicated as an adjunctive treatment for symptoms associated with panic disorder or posttraumatic stress disorder (PTSD), to be used under the direction of a health care professional, together with other pharmacological and/or nonpharmacological interventions.[1] It received 510(k) Premarket Notification clearance from the US Food and Drug Administration (FDA) in 2018.[1] Freespira is described by its manufacturer as a capnometry-guided respiratory intervention, which leads the user through guided and monitored breathing exercises.[1] Freespira is a software-hardware combination system that consists of a nasal cannula, a portable sensor that measures respiratory rate and exhaled carbon dioxide, and a dedicated tablet computer preloaded with the Freespira application (app).[1] Patients are instructed to engage in twice-daily, 17-minute tone-guided breathing exercises using standard biofeedback concepts to become aware of their breathing patterns and regulate their respiratory rates.[2]

Key Questions

KQ1. What is the clinical effectiveness of Freespira for individuals with panic disorder or PTSD?

KQ2. Does clinical effectiveness vary by condition (i.e., panic disorder without agoraphobia, panic disorder with agoraphobia, or PTSD), patient characteristics (e.g., age, sex), disease characteristics (e.g., severity, time since diagnosis, comorbidities), provider characteristics, or setting?

KQ3. What are the harms of Freespira for individuals with panic disorder or PTSD?

KQ4. Do the harms vary by condition (i.e., panic disorder without agoraphobia, panic disorder with agoraphobia, or PTSD), patient characteristics (e.g., age, sex), disease characteristics (e.g., time since diagnosis), provider characteristics, or setting?

KQ5. What are the costs or cost-effectiveness studies related to providing Freespira for individuals with panic disorder or PTSD?

KQ6. What are clinical practice guideline recommendations for the use of Freespira or other prescription digital therapeutics for individuals with panic disorder or PTSD?

KQ7. What are relevant Medicaid program coverage policies and private payer policies for the use of Freespira or other prescription digital therapeutics for individuals with panic disorder or PTSD?

Methods

Researchers from the Center for Evidence-based Policy (Center) searched Ovid MEDLINE, Cochrane Database of Systematic Reviews via the Cochrane Library, and other databases and information sources for randomized controlled trials (RCTs), nonrandomized comparative trials, prospective cohort studies, interrupted time series with comparison groups, before-after studies, cost and cost-effectiveness studies, and evidence-based clinical practice guidelines. Using a priori criteria, we conducted dual independent title and abstract screening and full-text article review for articles published in the English language. Two researchers assessed the included studies for risk of bias using standard forms. A third researcher settled discrepancies as needed.

We applied the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) approach to rate the certainty of evidence for each outcome.

We also searched 10 state Medicaid program websites, 13 private payer websites, and the Medicare Coverage Database for coverage determinations of Freespira and biofeedback. We also searched for biofeedback coverage determinations because Freespira uses biofeedback techniques for breathing retraining.[1,2]

Summary of Clinical Evidence and Recommendations Findings

We identified 3 eligible studies[3-5] that investigated the effectiveness of Freespira for panic disorder and PTSD; each of the studies were assessed as being at high risk of bias with no control group comparison and having only a small study sample. We did not identify any eligible studies that compared Freespira to a control group (i.e., standard care, sham treatment, no treatment). Table 1 presents a summary of findings for Freespira. Full details of the GRADE assessment are provided in Appendix F.

Table 1. Summary of Findings (GRADE)

Outcome	Number of Participants and Studies	Certainty of Evidence	Relationship	Rationale for Certainty of Evidence Rating
Symptom reduction	3 single-arm cohort studies[3-5] N = 176	●○○○ VERY LOW	Freespira was associated with improvement in both panic disorder and PTSD symptoms.	Downgraded 2 levels for study design (i.e., no comparator), 1 level for risk of bias, and 1 level for imprecision (i.e., small sample sizes).
Adherence	3 single-arm cohort studies[3-5] N = 176	●○○○ VERY LOW	Freespira was associated with: • An average adherence of 84% (SD 18%) amongst individuals with panic disorder. • An average adherence of 77% amongst individuals with PTSD.	Downgraded 2 levels for study design (i.e., no comparator), 1 level for risk of bias, and 1 level for imprecision (i.e., small sample sizes).
Serious adverse events	2 single-arm cohort studies[4,5] N = 124	●○○○ VERY LOW	Freespira was not associated with any serious adverse events.	Downgraded 2 levels for study design (i.e., no comparator), 1 level for risk of bias, and 1 level for imprecision (i.e., small sample sizes).
Hospitalization or ED use	None	NA	NA	NA
Quality of life	None	NA	NA	NA

Note. For methods and interpretation of GRADE ratings, see Appendix C.
Abbreviations. CI: confidence interval; ED: emergency department; GRADE: Grading of Recommendations, Assessment, Development, and Evaluations approach; NA: not applicable; PTSD: posttraumatic stress disorder.

Cost and Cost-Effectiveness

We did not identify any cost-effectiveness studies for Freespira; however, we did identify 1 cost-impact study using data from a claims-based study to investigate if treatment with Freespira would reduce medical costs for panic disorder.[3] Results from this study, assessed to be at high risk of bias and having limited generalizability, suggested that treatment of panic disorder with Freespira reduced medical costs by 35% in the 12 months post-treatment compared to the 12 months pre-treatment. This included all medical claims for physician visits, emergency department visits, and diagnostic tests. This study had no comparison group, so we have substantial uncertainty about how the use of Freespira relates to medical costs.

Clinical Practice Recommendations

A clinical practice guideline informed by a systematic review was published in 2023 by the Department of Veterans Affairs/Department of Defense and concluded that there is insufficient evidence to recommend for or against Freespira or other nonpharmacological biological therapies for the treatment of PTSD.[6] We did not identify any clinical practice guidelines that specifically referenced Freespira for the treatment of panic disorder. Other identified clinical guidelines for panic disorder or PTSD focused on psychological and pharmacological therapies and did not address Freespira, biofeedback-based approaches in general, or breathing retraining.[7-13] No guidelines were identified that addressed use of prescription digital therapeutics in general for either condition.

Key Policy Findings

We identified coverage policies related to Freespira from 4 private payers and 1 Medicaid program: Aetna, Anthem Blue Cross and Blue Shield (formerly Empire BlueCross BlueShield), Highmark Inc., Molina Healthcare, and the Medicaid program in Oregon (Oregon Health Plan).[14-20] Among the 5 payers that had policies that mentioned Freespira, 1 payer had partnered with the manufacturer to cover this digital therapeutic (Highmark Inc.).[21,22] One of the studies[3] included in the clinical evidence review reported the results of a quality improvement program conducted through Highmark Health, a health organization that includes health insurance plans (e.g., Highmark Blue Cross Blue Shield of Northeastern New York) and health care delivery (e.g., Allegheny Health Network).[21,23] The authors of this study worked for the Allegheny Health Network and recruited patients within this network who had health insurance coverage from Highmark Blue Cross Blue Shield, which provides health care benefits for people in western, north central, and northeastern Pennsylvania.[3] The 4 payers that did not cover Freespira considered the product experimental, investigational, and unproven.[14-16,20]

We identified coverage policies on biofeedback from the Centers for Medicare & Medicaid Services, as well as 5 private payers and 7 Medicaid programs: Aetna; Anthem Blue Cross and Blue Shield (formerly Empire BlueCross BlueShield); Cigna Healthcare; Excellus BlueCross BlueShield; Highmark Inc.; and the Medicaid programs in California (Medi-Cal), Massachusetts (MassHealth), New Jersey (NJ FamilyCare), New York, Oregon (Oregon Health Plan), Texas, and Washington State (Apple Health).[24-41] One of the 13 payers (Highmark Inc.) that had policies on biofeedback covered this service for patients with panic disorder or PTSD.[33] Biofeedback (Current Procedural Terminology code 90901, biofeedback training by any modality) was on the New York State Department of Health list of never pay procedures under ambulatory patient group reimbursement.[35]

Conclusions

Evidence related to Freespira was limited to a small number of non-comparative studies. These uncontrolled studies found that Freespira was associated with an improvement in symptoms of PTSD or panic disorder, it is not associated with serious adverse events, and the majority of patients are adherent to the treatment protocol. However, our confidence in the evidence is very low for any of these findings, and we expect that adequately controlled research would change these findings. The limited number of trials, lack of control groups, small sample sizes, and high risk of bias should be considered when drawing conclusions about the certainty of evidence for Freespira for the treatment of panic disorder and PTSD. Overall, we have very low certainty in these results, and new research is likely to change our understanding of Freespira for panic disorder and PTSD.

Background

Description of the Conditions

Panic Disorder

In the fifth edition text revision of the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-5-TR*), panic disorder is classified as an anxiety disorder.[42] According to the *DSM-5-TR*, anxiety disorders "share features of excessive fear and anxiety and related behavioral disturbances."[42] Panic disorder is defined as recurrent unexpected panic attacks not attributable to the physiological effects of a substance or other medical condition.[42] Panic disorder can occur with or without agoraphobia; if agoraphobia is present, a separate diagnosis of agoraphobia is given.[42] Panic attacks are characterized by an abrupt surge of intense fear or discomfort that reaches a peak within minutes.[42] During a panic attack, individuals may experience palpitations, increased heart rate, sweating, trembling, sensations of shortness of breath, and other uncomfortable symptoms.[42] Surveys have shown the lifetime and 12-month prevalence of panic disorder, with or without agoraphobia, in the US to be 3.8% and 2.7%, respectively.[43,44] Data collected from surveys conducted in 25 high- to lower-middle-income countries, including the US, showed that female gender, age less than 60 years, lower education, and low household income were associated with panic disorder.[43]

Researchers have proposed a connection between panic attacks and hyperventilation, characterized by low levels of carbon dioxide in the body due to an imbalance between oxygen inhaled and carbon dioxide exhaled.[45] High levels of carbon dioxide usually correspond to low levels of oxygen in the body and therefore serve as a warning that an individual may be at risk for imminent suffocation.[45] The carbon dioxide threshold may be lowered in people with panic disorder, causing activation of the brain's suffocation monitor at lower levels of carbon dioxide than for individuals without panic disorder, triggering shortness of breath and hyperventilation.[45,46] The Mental Health First Aid program recommendations include several breathing-focused steps for first aid providers working with individuals in the midst of panic attacks.[47] First aid providers are advised to help the person get their breathing under control by encouraging them to slow their breathing gradually and take slow and even breaths.[47]

Posttraumatic Stress Disorder

In the *DSM-5*, published in 2013, posttraumatic stress disorder (PTSD) was removed from the anxiety disorders category and placed in a new diagnostic category: trauma and stressor-related disorders.[48] This category is unique among psychiatric conditions in the requirement for exposure to a stressful event as a precondition.[48] PTSD is the development of a constellation of symptoms in response to a traumatic event.[42] According to the *DSM-5-TR*, the following criteria are required for diagnosis of PTSD in individuals older than 6 years of age:[42]

- Exposure to actual or threatened death, serious injury, or sexual violence
- Presence of one or more intrusion symptoms (e.g., recurrent, involuntary memories of the event; recurrent dreams of the event; flashbacks) associated with the traumatic event, beginning after the event occurred
- Persistent avoidance of stimuli associated with the traumatic event
- Negative alterations in cognition and mood associated with the traumatic event
- Marked alterations in arousal and reactivity associated with the traumatic event

- Duration of disturbance more than 1 month
- Disturbance causes significant distress or impairment in social, occupational, or other areas of functioning
- Disturbance is not attributable to physiological effects of a substance (e.g., medication, alcohol) or other medical condition

Surveys have shown the lifetime prevalence of PTSD in the US ranges from 5.7% to 9.4%, with 12-month prevalence ranging from 3.7% to 5.3%.[44,49] A survey of US veterans reported a lifetime prevalence of 8.1%.[50] Like panic disorder, PTSD is more common among females and individuals who are less than 65 years of age.[50,51] While provocation of panic attack symptoms during carbon dioxide challenge tests was initially only reported for panic conditions, it has been subsequently reported in individuals with established PTSD as well.[4]

Treatment

Treatment is indicated for most patients with panic disorder or PTSD.[52,53] Management of these conditions is based on patient preference, severity of symptoms, presence of coexisting conditions (e.g., substance use disorder), response to previous treatment, and cost and availability of treatment.[52] Treatment typically consists of a combination of psychotherapy (e.g., cognitive behavioral therapy, eye movement desensitization and reprocessing) and pharmacotherapy (e.g., selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors, tricyclic antidepressants) with or without complementary therapies such as exercise, yoga, and mindfulness-based interventions.[52-55]

Biofeedback is a treatment method that uses a biomonitoring system to measure a physiological process that is normally involuntary, such as heart rate, blood pressure, or muscle tension, and provides feedback about that process to an individual.[30,56,57] The individual uses this information to learn how to gain voluntary control over and modify these physiological processes.[30,56] Capnometry is a noninvasive method of measuring the concentration or partial pressure of carbon dioxide in exhaled air (end-tidal carbon dioxide ($ETCO_2$).[58] Capnometry-based biofeedback trains patients to use serial $ETCO_2$ values to adjust their respiratory pattern to bring their $ETCO_2$ values closer to baseline.[59]

Barriers to treatments for individuals with panic disorder or PTSD include failure to diagnose the condition, failure to recognize a need for treatment, and lack of access to qualified mental health professionals.[60,61] Military personnel and veterans may fail to seek treatment for PTSD because of the perception that doing so may negatively affect their career trajectory and because vulnerability is antithetical to the warrior mentality.[60] Data from the US National Comorbidity Survey Replication showed that among individuals with an anxiety disorder (according to *DSM*-IV classification and therefore including both PTSD and panic disorder), 58% perceived a need for treatment, 42% had received any treatment over a 12-month period, and 16% had received possibly adequate treatment over a 12-month period.[61] The authors of this study, which included survey data from 21 countries, concluded that gaps existed among individuals with anxiety disorders perceiving a need for treatment and receiving adequate treatment.[61] A study of patients attending Massachusetts General Hospital for any reason who had recently been diagnosed with PTSD found that 28% of patients had not received any treatment for PTSD, 19% had been prescribed medication alone, 28% had undergone therapy alone, and 25% had both

therapy and medication.[62] In this study, individuals with Medicaid had a 35% lower likelihood of participating in at least 12 therapy sessions (which was used as a proxy for receiving a full course of therapy) than did individuals with private insurance.[62]

Freespira

Based on the recognition of subtle respiratory irregularities associated with hyperventilation and carbon dioxide sensitivity in panic disorder sufferers, Meuret and colleagues (2008) investigated a capnometry-guided respiratory biofeedback intervention in 37 participants.[63] Treatment focused on normalizing both respiratory rate and $ETCO_2$, which is the level of carbon dioxide released at the end of an exhalation.[63] Capnometry is the noninvasive measurement of exhaled carbon dioxide; it provides a numerical value for $ETCO_2$.[64] The intervention described by Meuret and colleagues provided breath-to-breath feedback of $ETCO_2$ while modeling paced breathing at 4 different respiratory rates.[63] Administered as twice-daily, 17-minute sessions over a 4-week period, the authors reported that by study end, 86% of participants reported zero weekly panic attacks; improvement was durable over time, with 73% reporting zero weekly attacks at 1-year post-treatment.[63] Although this RCT was designed with a waitlist control, the waitlist group also received active treatment after the first 28 days.[63] Outcomes reported at the end of this study were for the entire cohort of enrolled patients, all of whom received the active treatment, with no comparator.[63] The biofeedback system designed by Meuret and colleagues was the basis for the product now known as Freespira.[2] No studies related to Freespira or its predicates address potential for relapse or explore long-term duration of effect beyond the follow-up period in the studies.[3-5,63,65,66]

Freespira is a digital therapeutic biofeedback device indicated as an adjunctive treatment of symptoms associated with either panic disorder or PTSD, to be used under the direction of a health care professional, together with other pharmacological or nonpharmacological interventions.[1] It received 510(k) Premarket Notification clearance from the US Food and Drug Administration (FDA) in 2018.[1] Freespira is described by its manufacturer as a capnometry-guided respiratory intervention.[1] It consists of a nasal cannula, a portable sensor that measures respiratory rate and exhaled carbon dioxide, and a dedicated tablet preloaded with the Freespira application (app). The tablet is locked down so that it can only be used with the Freespira program.[67] Freespira incorporates the treatment protocol described above as patients are trained to use the Freespira sensor and the Freespira app to measure and display their $ETCO_2$ levels.[1] Patients are instructed to engage in twice-daily, 17-minute tone-guided breathing exercises that are intended to normalize dysfunctional breathing over a 28-day period.[1,3,5] The sensor and tablet are returned to Freespira when treatment ends, where they are refurbished and used for other patients.[67]

FDA Approval of Freespira

The 510(k) pathway allows medical device manufacturers to receive marketing approval for their device by demonstrating that their product is "substantially equivalent" to one or more approved FDA devices.[68] According to the FDA website, a device is "substantially equivalent" to a predicate if it:

- Has the same intended use as the predicate; and
- Has the same technological characteristics of the predicate; or
- Has the same intended use as the predicate; and

- Has different technological characteristics and does not raise different questions of safety and effectiveness; and
- The information submitted to FDA demonstrates that the device is as safe and effective as a legally marketed device."[68]

For a 510(k) pathway review, FDA staff evaluates the similarity of the new device to the predicate device.[68] Submission of clinical trial data is not required for a 510(k) pathway application.[69]

The 510(k) pathway is the most widely used FDA regulatory pathway for medical devices; of more than 155,000 medical devices cleared by the FDA since 1976, approximately 99% have used the 510(k) pathway.[70,71] Among digital therapeutics 1 study found that nearly two-thirds of FDA reviewed products used the 510(k) pathway.[72] Devices that are reviewed though the 510(k) pathway are considered FDA-cleared devices.[73]

Freespira received 510(k) Premarket Notification clearance from the FDA in 2018.[1] The manufacturer, Palo Alto Health Sciences, cited the Canary Breathing System as a predicate device.[1] The Canary Breathing System was also manufactured by Palo Alto Health Sciences and had received 510(k) clearance in 2013 as a device used to provide biofeedback-based respiratory training to patients with panic disorder.[74] The only substantial difference between Canary Breathing System and Freespira is the expanded indication for PTSD and modifications that allowed the device to be used while plugged into an alternating current (AC) power adapter.[1] Table 2 describes the predicate devices and research studies referenced in Freespira-related 510(k) applications. In the 510(k) process, predicates are devices that the applicant proposes are substantially similar in some way to the applicant's device.[75] Predicates are not required to have the same indication or to be identical to the applicant device.[75] The 510(k) application for Canary Breathing System cites a similar biofeedback device used for breathing training in individuals with high blood pressure and a portable capnometer used in emergency medicine and respiratory care as predicate devices.[74]

Table 2. Predicate Devices Referenced in Freespira FDA 510(k) Applications

Device Name Applicant Clearance Date	Indication	Predicate(s)	Cited Research
Canary Breathing System Palo Alto Health Sciences K131586 December 10, 2013	Adjunctive treatment of symptoms associated with panic disorder, to be used under the direction of a health care professional	RESPeRATE (InterCure Inc.) • Canary device is substantially similar to existing biofeedback device used for breathing training for patients with high blood pressure LoFlo C5 (Respironics Novametrix LLC) • Capnometer used to measure breathing rate and $EtCO_2$ in Canary device is substantially similar to an existing portable capnometer used to monitor carbon dioxide recovery in emergency medicine	Meuret AE, et al. Feedback of end-tidal pCO_2 as a therapeutic approach for panic disorder. *J Psychiatr Res*. 2008;42(7);560-568.[63] Meuret AE, et al. Changes in respiration mediate changes in fear of bodily sensations in panic disorder. *J Psychiatr Res*. 2009;43(6):634-641.[65] Meuret AE, et al. Respiratory and cognitive mediators of treatment change in panic disorder: evidence for intervention specificity. *J Consult Clin Psychol*. 2010;78(5):691-704.[66]

Device Name Applicant Clearance Date	Indication	Predicate(s)	Cited Research
Freespira Palo Alto Health Sciences K180173 August 23, 2018	Adjunctive treatment of symptoms associated with panic disorder or PTSD, to be used under the direction of a health care professional	Canary Breathing System (same device, with added indication of PTSD and new ability to be used while plugged into AC power adapter)	Refers to clinical study of use of device in patients with PTSD described in Ostacher et al., (2021)[4] but does not provide citation.

Abbreviations. AC: alternating current; $EtCO_2$: end-tidal carbon dioxide; FDA: US Food and Drug Administration; pCO_2: partial pressure of carbon dioxide; PTSD: posttraumatic stress disorder.

Freespira, which is intended to be used as an adjunct treatment for panic disorder and PTSD, is considered a digital therapeutic. Digital therapeutics are health software intended to treat or alleviate a disease, disorder, condition, or injury by generating and delivering a medical intervention. Digital therapeutics may or may not require a prescription; analysts say the decision to make a product require a prescription appears to be related to the manufacturer's marketing strategy.[76,77] Freespira's 510(k) FDA clearance document indicates that the product would require a prescription,[78] but more recent information suggests that Freespira requires authorization from a licensed health care provider but no longer requires a clinician's prescription.[79]

Policy Issues

Policy references to Freespira variably mention the product under prescription digital therapeutics, mobile device-based health management applications, digital health technologies, or digital therapeutic products. At present, there are no federal requirements for coverage of digital therapeutics or digital diagnostics by Medicaid, although multiple bills have been put before Congress.[80-83] The most recent, the Access to Prescription Digital Therapeutics Act of 2023 (HR 1458 and S 723), was introduced in March 2023.[81,82] The bill proposes Medicare and Medicaid coverage of prescription digital therapeutics and would require the Centers for Medicare & Medicaid Services (CMS) to establish a payment methodology for prescription digital therapeutics, assign product-specific Healthcare Common Procedure Coding System (HCPCS) codes for these products, and create a system for manufacturer reporting. The latest action occurred on September 19, 2023, when HR 1458 was on the agenda for a subcommittee meeting.[81]

The first HCPCS code for a prescription digital therapeutic became effective in April 2022.[84] This Level II code, A9291, was created in response to a request from the manufacturer of reSET, a prescription digital therapeutic for the management of individuals with substance use disorder. The code describes "prescription digital behavioral therapy, fda [*sic*] cleared, per course of treatment."[84(p46)] This language was later modified to "prescription digital cognitive and/or behavioral therapy."[85(p75)] At the public meeting where this new code was discussed, the primary speaker for the application noted that the American Medical Association had elected to include

digital cognitive behavioral therapy in the existing codes for remote therapeutic monitoring.[84] The speaker observed that this Current Procedural Terminology (CPT) code change did not create a billing pathway for prescription digital therapeutics because the cognitive behavioral therapy remote therapeutic monitoring supply code is for FDA-cleared devices prescribed by a physician who has incurred a cost, taken ownership or title of the device, and billed for the device, qualifications that did not apply to prescription digital therapeutics.[84]

Since the establishment of code A9291, two additional HCPCS Level II codes for prescription digital therapeutics have been created: A9292, to describe a prescription digital therapeutic to improve visual acuity in patients with amblyopia (October 2023),[85] and A9293, to describe a prescription digital therapeutic to monitor fertility (April 2024).[86] In 2022, CMS determined that digital therapies or computer software housed on non-medical devices, such as smartphones or computers, and the equipment and software as a whole are not durable medical equipment and therefore would not fall under a Medicare Durable Medical Equipment, Prosthetic Devices, Prosthetics, Orthotics, and Supplies (DMEPOS) benefit category.[87,88]

Biofeedback, including modalities using capnometry, is on the Veterans Health Administration's approved list of complementary and integrative health approaches.[89,90] Services on this list must be made available to veterans when considered clinically necessary by their care team. In 2019, the Veterans Affairs Evidence Synthesis Program published an evidence map on guided imagery, biofeedback, and hypnosis.[91] The authors included systematic reviews investigating the populations for which these interventions had been used and their effectiveness and harms.[91] The 16 systematic reviews identified on biofeedback examined the use of this intervention for a variety of conditions including chronic constipation, fecal or urinary incontinence, headache, and stroke.[91] Panic disorder and PTSD were not mentioned in these included systematic reviews, and these conditions were not mentioned in the overall discussion of biofeedback in the evidence map.[91]

In June 2023, Lovell Government Services, a service-disabled veteran-owned small business, announced a partnership with Freespira.[92] This partnership provides a mechanism for federal health care systems (such as the Veterans Health Administration, the Military Health System, and Indian Health Services) to provide access to Freespira. Freespira is available on GSA Advantage, the US General Services Administration online marketplace for government agencies, at the cost of $2,750.[93]

Contextual Questions

CQ1. *How do Freespira or other prescription digital therapeutics fit into the overall management of individuals with panic disorder or PTSD? What are considerations for patient selection, monitoring, and follow-up after the 28-day course of Freespira?*

Digital therapeutics are health software intended to treat or alleviate a disease, disorder, condition, or injury by generating and delivering a medical intervention that has a demonstrable positive therapeutic impact on a patient's health. Digital therapeutics may be used independently or in concert with medications, devices, or other therapies to optimize patient care and health outcomes. Digital therapeutics may or may not require a prescription and are generally considered medical devices subject to regulatory oversight by the FDA. Freespira is a digital

therapeutic biofeedback device indicated as an adjunctive treatment of symptoms associated with panic disorder or PTSD, to be used under the direction of a health care professional, together with other pharmacological or nonpharmacological interventions.[1] However, neither psychotherapy nor medications are required for patients using Freespira. Authorization from a licensed health care provider is required, but a prescription from a physician is not necessary. Freespira is currently the only FDA-cleared digital therapeutic indicated for the treatment of panic disorder and PTSD symptoms.

Patients have two pathways to access Freespira: self-referral through Freespira's website or referral from a health care provider. Once referred, patients will engage with a Freespira advisor to verify benefits and validate the patient meets clinical criteria. If health care providers are referring a patient to Freespira, there are a few important considerations to keep in mind for patient selection:

- Access to internet: A primary barrier to using digital therapeutics is ensuring access to required technologies and reliable internet connectivity. Limited access to broadband internet often impacts individuals in rural areas, but individuals located in urban and suburban areas can experience similar barriers. Freespira does not require sustained internet access to operate, but it does need an internet connection for updates and for uploading data to the Freespira server for review by health coaches and health care providers.
- Digital and health literacy: Individuals' understanding of common health technologies and ability to use digital technologies vary greatly and cannot be assumed simply from a person's age, cultural background, or geographic location.
- Cultural and linguistic appropriateness: When providing a digital therapeutic, it is important to consider if it is available in the individual's native language, and whether the digital therapeutic has been validated with the user population.
- Risks and warnings: Freespira is not indicated for patients who are younger than 13 years old, are pregnant, or have chronic obstructive pulmonary disease (COPD) or emphysema.

CQ2. *What are health equity considerations for providing Freespira or other prescription digital therapeutics for individuals with panic disorder or PTSD?*

While most experts believe the expected harms of digital health technologies like Freespira are limited, these may include issues related to data (e.g., not keeping patient data secure or selling patient data without notification),[94-97] offering inaccurate or ineffective information or treatment,[94,98] problems related to software defects,[95,99,100] lack of transparency in AI algorithms,[101] and concerns about patient consent and autonomy.[101] Researchers raised additional health equity concerns for digital health technologies, such as whether product content is available in multiple languages and is culturally appropriate for diverse populations,[73,97,102-104] if there will be equitable access to internet services and required devices,[73,97,104,105] and if the technologies have been adequately studied in diverse populations.[72] Commentators also note potential for conflicts of interest in research on commercialized products.[106] Because enthusiasm for use of digital technologies may outpace the evidence, there is also potential for harm due to reduced use of existing evidence-based practices.[106]

Disenfranchised groups in the US have disproportionate exposure to trauma and disparities in access to treatment.[107,108] Similarly, there are racial-ethnic disparities in both access to and quality of mental health services for Black Americans with panic disorder in comparison with

White Americans.[109,110] While digital therapeutics may have the potential to reduce disparities by allowing access to evidence-based therapies remotely and privately,[111] we did not identify any research addressing the impact of prescription digital therapeutics like Freespira on access to care or reduction of health disparities related to either PTSD or panic disorder.

CQ3. *What are relevant recommendations or guidelines from national organizations about the selection and use of prescription digital therapeutics?*

The Center identified only 1 professional guideline or recommendation statement that addressed Freespira or prescription digital therapeutics for panic disorders or PTSD (see Methods and Appendix A for description of search methods and sources). The Department of Veterans Affairs (VA) and Department of Defense (DoD) published a clinical practice guideline for the management of PTSD in 2023, which included Freespira in a key question (KQ) related to effectiveness and safety of non-pharmacological biological treatments as primary treatments or adjuncts to standard treatment for improving PTSD symptoms.[6] The panel did not make any recommendations related to Freespira or other somatic therapies, citing insufficient evidence to recommend for or against such treatments.[6] The guideline does not contain any discussion of how prescription digital therapeutics in general, or Freespira in particular, could address issues related to access to treatment or health disparities.[6] No other recommendations or guidelines were identified that addressed the selection and use of prescription digital therapeutics for treatment of panic disorder or PTSD.

Methods

This review is based on KQs and contextual questions (CQs) identified by the New York State Department of Health. Search parameters, KQs and CQs, and methodologies for identifying, assessing, and reporting evidence are described in the following sections.

Key Questions

The following key questions are addressed in the clinical evidence review and payer policies section:

KQ1. What is the clinical effectiveness of Freespira for individuals with panic disorder or PTSD?

KQ2. Does clinical effectiveness vary by condition (i.e., panic disorder without agoraphobia, panic disorder with agoraphobia, or PTSD), patient characteristics (e.g., age, sex), disease characteristics (e.g., severity, time since diagnosis, comorbidities), provider characteristics, or setting?

KQ3. What are the harms of Freespira for individuals with panic disorder or PTSD?

KQ4. Do the harms vary by condition (i.e., panic disorder without agoraphobia, panic disorder with agoraphobia, or PTSD), patient characteristics (e.g., age, sex), disease characteristics (e.g., time since diagnosis), provider characteristics, or setting?

KQ5. What are the costs or cost-effectiveness studies related to providing Freespira for individuals with panic disorder or PTSD?

KQ6. What are clinical practice guideline recommendations for the use of Freespira or other prescription digital therapeutics for individuals with panic disorder or PTSD?

KQ7. What are relevant Medicaid program coverage policies and private payer policies for the use of Freespira or other prescription digital therapeutics for individuals with panic disorder or PTSD?

Contextual Questions

Information that we identified to answer the following contextual questions is summarized in the Background section:

CQ1. How do Freespira or other prescription digital therapeutics fit into the overall management of individuals with panic disorder or PTSD? What are considerations for patient selection, monitoring, and follow-up after the 28-day course of Freespira?

CQ2. What are health equity considerations for providing Freespira or other prescription digital therapeutics for individuals with panic disorder or PTSD?

CQ3. What are relevant recommendations or guidelines from national organizations about the selection and use of prescription digital therapeutics?

Eligible Studies

Table 3 summarizes the study inclusion and exclusion criteria. Further inclusion and exclusion criteria details can be found in Appendix B.

Table 3. Key Study Inclusion Criteria

Study Component	Inclusion Criteria
Populations	• Individuals aged 18 years or older diagnosed with panic disorder (with or without agoraphobia) or PTSD
Interventions	• Freespira (capnometry-guided respiratory intervention) digital therapeutic, with or without standard interventions (e.g., psychotherapy, pharmacotherapy)
Comparators	• Head-to-head comparisons with other prescription digital therapeutics • Standard care (e.g., pharmacotherapy, psychotherapy) • No comparison group
Outcomes	Critical • Change in symptoms related to panic disorder or PTSD • Treatment adherence Important • Hospitalization or emergency department use related to panic disorder or PTSD • Serious adverse events • Patient reported quality of life
Timing and follow-up	• Minimum follow-up of 1 month after the end of the intervention period
Setting	• Studies conducted in outpatient settings • Studies conducted in countries categorized as *very high* on the Human Development Index
Study design	KQ1 and KQ2 • RCTs • Nonrandomized comparative trials • Prospective cohort studies • Interrupted time series with comparison group • Controlled before-after studies • Uncontrolled before-after studies

Study Component	Inclusion Criteria
	KQ3 • Comparative studies and economic evaluations • Cost-effectiveness analyses • Economic modeling studies KQ4 • Evidence-based clinical practice guidelines that provide specific treatment recommendations
Sample size	• No limit
Publication type	• Peer-reviewed publication of primary study results • Published in the English language • Ancillary publications with additional comparative follow-up

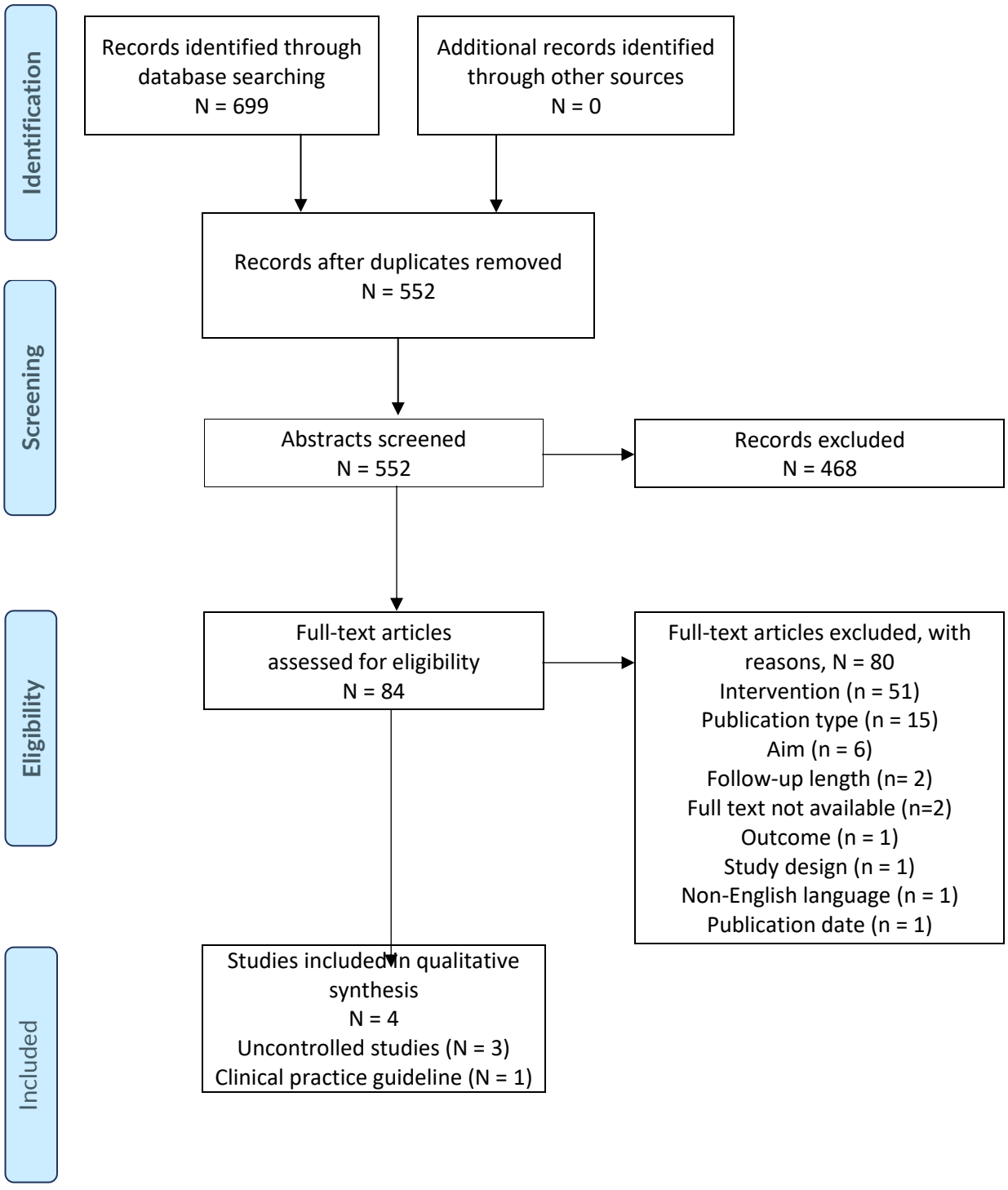
Abbreviations. KQ: key question; PTSD: posttraumatic stress disorder; RCT: randomized controlled trial.

Evidence and Policy Searches

Researchers from the Center for Evidence-based Policy (Center) searched Ovid MEDLINE, Cochrane Database of Systematic Reviews via the Cochrane Library, and other databases and information sources. Because we could not find any randomized controlled trials (RCTs), we expanded our search to include nonrandomized comparative trials, prospective cohort studies, interrupted time series with comparison groups, before-after studies, cost and cost-effectiveness studies, and evidence-based clinical practice guidelines. We identified 552 potentially relevant publications for the key questions for clinical evidence and clinical practice guidelines (Figure 2). We also searched trial registries for relevant ongoing trials. A full list of sources searched and the search strategies are listed in Appendix A. We did not conduct systematic searches to identify publications to answer contextual questions.

We also searched 10 state Medicaid program websites, 13 private payer websites, and the Medicare Coverage Database for coverage determinations of Freespira or biofeedback (due to Freespira's use of capnometry-based biofeedback). Five coverage policies that specifically mentioned Freespira were identified; 13 relevant coverage policies were identified for biofeedback. Appendix A lists search terms used to identify relevant policies, and all sources searched.

Figure 1. PRISMA Diagram With Details



Screening and Inclusion

Two researchers used the systematic review software platform DistillerSR to screen publications identified in the searches using the detailed inclusion and exclusion criteria listed in Appendix B. Disagreement about inclusion was resolved through discussion. Appendix D lists included studies, and Appendix H lists studies excluded during full-text screening along with the primary reason each study was excluded. Figure 1 shows the numbers of studies screened and included or excluded at each step.

Risk of Bias Assessment

Two researchers assessed each included study for risk of bias using standard forms. Appendix E has detailed tables with criteria considered for assessing risk of bias or methodological quality. Disagreement between the researchers was resolved through discussion.

Synthesis

We report a narrative synthesis of the clinical evidence and policy findings. We applied the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) system (Appendix F) to rate the overall quality of evidence for key outcomes and test performance. The GRADE system defines the overall quality of a body of evidence for an outcome in the following manner:

- **High (RCTs start here):** Raters are very confident that the estimate of the effect of the intervention on the outcome lies close to the true effect. Typical sets of studies are RCTs with few or no limitations, and the effect estimate is likely stable.
- **Moderate:** Raters are moderately confident in the estimate of the effect of the intervention on the outcome. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is different. Typical sets of studies include RCTs with some limitations or well-performed nonrandomized studies with additional strengths that guard against potential bias and have large estimates of effects.
- **Low (nonrandomized studies start here):** Raters have little confidence in the estimate of the effect of the intervention on the outcome. The true effect may be substantially different from the estimate of the effect. Typical sets of studies include RCTs with serious limitations or nonrandomized studies without special strengths.
- **Very low:** Raters have no confidence in the estimate of the effect of the intervention on the outcome. The true effect is likely to be substantially different from the estimate of the effect. Typical sets of studies include nonrandomized studies with serious limitations or inconsistent results across studies.
- **Not applicable:** Researchers did not identify any eligible studies.

Clinical Evidence Review

We identified 3 eligible studies that investigated the effectiveness of Freespira with no control group comparison and 1 clinical practice guideline. We did not identify any eligible studies that compared Freespira to a control group (i.e., standard care, sham treatment, no treatment). One of the included publications also incorporated a cost analysis. The FDA 510(k) application for Freespira's predecessor, Canary Breathing System,[2] explains that the FDA-cleared device uses methods "based on" capnometry-assisted respiratory training methods developed and tested by Meuret and colleagues,[63,65,66] but these studies are not included in the evidence review. While

the Meuret studies describe development of components of a biofeedback technique for breathing training (focusing on breathing patterns and practicing new breathing patterns with capnometry feedback), incorporation of the same tablet and sensor combination utilized by Freespira is not defined.[63,65,66]

KQ1: Effectiveness

Table 4 presents the characteristics of the 3 included studies, all of which were limited to adult participants.[3-5] All 3 studies had high risk of bias because of the lack of any control group. Two of the studies enrolled individuals with a primary diagnosis of panic disorder (N = 121),[3,5] while 1 of the studies enrolled individuals with a primary diagnosis of PTSD (N = 55).[4] While screening studies for inclusion in this review we also identified a larger real-world evidence effectiveness study (N = 1,569) that enrolled participants with both panic disorder (N = 1,395) and PTSD (N = 174);[112] however, this single-arm study did not have any follow-up beyond the 28-day Freespira treatment protocol and thus did not meet inclusion criteria for this review. This section of the report is organized by outcome, then by indication.

Table 4. Characteristics of Included Studies

Publication Author, Year Trial Identifier Study Location Study Design	Population Description N Enrolled Participants Participant demographics	Intervention Comparator Duration	Risk of Bias Outcomes of Interest Reported
Panic disorder			
Kaplan et al. 2020[3] None US Single-arm observational study *Note: This trial was conducted as part of a quality improvement program within the Alleghany Health Network and was not registered in any clinical trials database.*	Adults with a primary diagnosis of panic disorder and health insurance from Highmark BCBS of Western Pennsylvania Enrolled N = 52 Mean age 39 years (range 18 to 63) Gender 67% female	Intervention: Freespira Comparator: None Duration: 12 months	High risk of bias Outcomes • Symptom reduction • Adherence • Cost impact
Tolin et al. 2017[5] NCT01955954 US Single-arm observational study	Adults aged 18 to 65 years with a primary diagnosis of panic disorder Analyzed N = 69 Mean age 37 years (SD 11.0) Gender 59% female	Intervention: Freespira Comparator: None Duration: 12 months	High risk of bias Outcomes • Symptom reduction • Adherence • Adverse events

Publication Author, Year Trial Identifier Study Location Study Design	Population Description N Enrolled Participants Participant demographics	Intervention Comparator Duration	Risk of Bias Outcomes of Interest Reported
Posttraumatic stress disorder			
Ostacher et al. 2021[4] NCT03039231 US Single-arm observational study	Adults with a primary *DSM-5* diagnosis of PTSD who agreed (if on any psychotropic medication) to maintain their current stable dose from point of study entry until the 2-month post-treatment assessment Enrolled N = 55 Mean age 51 years (range, 19 to 77) Gender: 35% female	Intervention: Freespira Comparator: None Duration: 6 months	High risk of bias Outcomes • Symptom reduction • Adherence • Adverse events

Abbreviations. BCBS: Blue Cross Blue Shield; DSM-5: Diagnostic and Statistical Manual of Mental Disorders, *Fifth Edition; PTSD: posttraumatic stress disorder; SD: standard deviation.*

GRADE Summary of Effectiveness and Safety of Freespira

Table 5 presents a summary of the effectiveness and safety outcomes from the 3 eligible studies investigating Freespira. Detailed findings from those trials are described in the next section (Effectiveness and Safety) of this report.

Table 5. Summary of Findings (GRADE): Freespira

Outcome	Number of Participants and Studies	Certainty of Evidence	Relationship	Rationale for Certainty of Evidence Rating
Symptom reduction	3 single-arm cohort studies[3-5] N = 176	●○○○ VERY LOW	Freespira was associated with statistically significant and clinically meaningful improvement in both panic disorder and PTSD symptoms, relative to patient baseline, which were maintained at 12 months. However, without a control group, we cannot be certain if this effect was associated directly with Freespira use or reflective of the natural course of panic disorder and PTSD over time.	Downgraded 2 levels for risk of bias, and 1 level for imprecision (i.e., small sample sizes).
Adherence	3 single-arm cohort studies[3-5] N = 176	●○○○ VERY LOW	Freespira was associated with a high level of adherence (around 77% to 84%).	Downgraded 2 levels for risk of bias, and 1 level for imprecision (i.e., small sample sizes).

Outcome	Number of Participants and Studies	Certainty of Evidence	Relationship	Rationale for Certainty of Evidence Rating
Serious adverse events	2 single-arm cohort studies[4,5] N = 124	●○○○ VERY LOW	There were no reports of serious adverse event with Freespira use.	Downgraded 2 levels for risk of bias, and 1 level for imprecision (i.e., small sample sizes).
Hospitalization or ED use	No eligible studies reported this outcome			
Quality of life	No eligible studies reported this outcome			

For methods and interpretation of GRADE ratings, see Appendix C.

Abbreviations. CI: confidence interval; ED: emergency department; GRADE: Grading of Recommendations, Assessment, Development, and Evaluations approach; NA: not applicable; PTSD: posttraumatic stress disorder.

Change in Symptoms

We reviewed reported changes in panic disorder and PTSD symptoms that were measured by validated tools (i.e., Panic Disorder Severity Scale [PDSS], Sheehan Disability Scale [SDS], and Clinical Global Impression – Severity Scale). Table 6 describes these tools in further detail.

Table 6. Measuring Changes in Symptoms: Validated Tools

Tool	Description	Score Range	Clinical Interpretation
Panic Disorder Severity Scale (PDSS)	A 7-item structured interview, with each item rated on a scale from 0 to 4.	0 to 28; higher scores indicating greater severity	• Response defined as PDSS percent reduction ≥ 40% • Remission defined as absolute PDSS scores of ≤ 5
Sheehan Disability Scale (SDS)	A 3-item self-rated questionnaire that assesses functional impairment in work/school, social life, and family life, with each item rated on a scale from 0 to 10.	0 to 30; higher scores indicate greater functional impairment	• Remission defined as SDS scores of ≤ 5 • Scores of ≥ 5 on any of the 3 items are associated with significant functional impairment
Clinical Global Impression – Severity Scale (CGI-S)	A single-item, observer-rated subscale, rated on a scale from 1 to 7. Clinicians rate the severity of the patient's illness at the time of assessment, relative to the clinician's past experience with patients who have the same diagnosis.	1 to 7; higher scores indicate greater severity of mental illness	1 = Normal, not at all ill 2 = Borderline mentally ill 3 = Mildly ill 4 = Moderately ill 5 = Markedly ill 6 = Severely ill 7 = Extremely ill

Tool	Description	Score Range	Clinical Interpretation
Clinician-Administered PTSD Scale (CAPS-5)	A 30-item structured interview, with each item rated on a scale from 0 to 4.	0 to 80, calculated using the sum of the first 20 items; higher scores indicate more severe PTSD	The *DSM-5* PTSD diagnostic rule requires: • At least 1 Criterion B symptom (items 1-5) • At least 1 Criterion C symptom (items 6-7) • At least 2 Criterion D symptoms (items 8-14) • At least 2 Criterion E symptoms (items 15 to 20) • Criterion F is met (disturbance has lasted 1 month) • Criterion G is met (disturbance causes either clinically significant distress or functional impairment)

Abbreviations. CGI-S: Clinical Global Impression – Severity Scale; DSM-5: Diagnostic and Statistical Manual of Mental Health, Fifth Edition; PDSS: Panic Disorder Severity Scale; PTSD: posttraumatic stress disorder; SDS: Sheehan Disability Scale.

Panic Disorder

We identified 2 studies[3,5] reporting changes in panic disorder symptoms associated with the completion of the 28-day Freespira protocol (Table 7 and Table G1). Overall, the direction of effect was consistent between both studies. Immediately post-treatment and at 12 months, both studies found the following:

- There were significant decreases in panic disorder symptoms, as measured by the Panic Disorder Severity Scale, Sheehan Disability Scale, and Clinical Global Impression – Severity Scale (Table 6).
- The majority of the participants were considered responders (defined as ≥ 40% reduction in Panic Disorder Severity Score) immediately after completion of the active protocol and through the 12 months of follow-up.
- The majority of participants were in remission (defined as a Panic Disorder Severity Score < 5) after completion of treatment and remained in remission during the 12 months of follow-up.

Table 7. Summary of Change in Panic Disorder Symptoms

Author, Year Risk of Bias	Findings
PDSS score	
Kaplan et al., 2020[3] High risk of bias	Mean PDSS score reduced significantly from 14.4 at baseline to 4.9 post-treatment ($P < .01$). This reduction was maintained at 6 months (mean score, 4.1) and at 12 months (mean score, 4.4; both $P < .01$ from baseline).
Tolin et al., 2017[5] High risk of bias	Mean PDSS score reduced significantly from 14.9 at baseline to 5.4 post-treatment ($P < .01$). This reduction was maintained at 2 months (mean score, 6.1)

Author, Year Risk of Bias	Findings
	and at 12 months (mean score, 5.4; both *P* < .01 from baseline). The decrease from baseline was statistically significant, and classified as a large effect using Cohen's *d*.
Sheehan Disability Scale	
Kaplan et al., 2020[3] High risk of bias	From baseline, mean scores on the SDS declined from 14.7 to 5.9 post-treatment (P < .01). This reduction was maintained at 6 months (mean score, 3.8) and at 12 months (mean score, 5.0; *P* < .01).
Tolin et al., 2017[5] High risk of bias	Mean SDS score reduced from 14.8 at baseline to 7.7 post-treatment. This reduction was maintained at 2 months (mean score, 6.4) and at 12 months (mean score, 5.7). The significance of the decrease from baseline was not reported, but the decrease was classified as a large effect using Cohen's *d*.
Clinical Global Impression – Severity Scale	
Kaplan et al., 2020[3] High risk of bias	From baseline, mean scores on the CGI-S declined from 4.4 to 2.8 post-treatment. This reduction was maintained at 6 months (mean score, 2.1) and at 12 months (mean score, 2.1). Statistical significance was not reported.
Tolin et al., 2017[5] High risk of bias	Mean CGI-S score reduced from 4.5 at baseline to 2.7 post-treatment. This reduction was maintained at 2 months (mean score, 2.5) and at 12 months (mean score, 2.1). The significance of the decrease from baseline was not reported, but the decrease was classified as a large effect using Cohen's *d*.
Response, defined as a 40% reduction or more in PDSS score	
Kaplan et al., 2020[3] High risk of bias	In a completer analysis, 82% of participants (36 of 44) were classed as responders post-treatment, 85% (23 of 27) at 6 months, and 91% (20 of 22) at 12 months.
Tolin et al., 2017[5] High risk of bias	In an intent-to-treat analysis, 83% of participants (57 of 69) were classed as responders post-treatment, 72% (50 of 69) at 2 months, and 77% (53 of 69) at 12 months.
Remission, defined as a PDSS score of 5 or less	
Kaplan et al., 2020[3] High risk of bias	No participant was classed as being in remission at baseline using the PDSS score. In a completer analysis, 48% of participants (21 of 44) were classed as being in remission post-treatment, 74% (23 of 27) at 6 months, and 68% (15 of 22) at 12 months.
Tolin et al., 2017[5] High risk of bias	In an intent-to-treat analysis, 54% of participants (37 of 69) were classed as responders post-treatment, 53% (37 of 69) at 2 months, and 59% (41 of 69) at 12 months.

Abbreviations. CGI-S: Clinical Global Impression – Severity Scale; NA: not applicable. NR: not reported; PDSS: Panic Disorder Severity Scale; SDS: Sheehan Disability Scale.

Posttraumatic Stress Disorder

One study reported[4] changes in PTSD symptoms associated with the completion of the 28-day Freespira protocol (Table 8 and Table G2). Overall the direction of effect was similar to that seen in the panic disorder studies. The study found the following:

- There were decreases in PTSD symptoms, as measured by the panic disorder Severity Scale, Sheehan Disability Scale, and Clinical Global Impression – Severity Scale immediately post-treatment and at 2 and 6 months.

- At month 2, 88% of participants had responded (defined as a ≥6-point reduction in CAPS-5 score) to treatment (primary efficacy outcome).
- At month 2, 48% of participants were in remission (defined as CAPS-5 score < 25 and no longer meeting *DSM-5* criteria for PTSD), and at month 6, 50% of participants were in remission.

Table 8. Summary of Change in Posttraumatic Stress Disorder Symptoms

Author, Year Risk of Bias	Findings
Clinician Administered PTSD Scale (CAPS-5) score	
Ostacher et al., 2021[4] High risk of bias	Mean CAPS-5 scores decreased from 49.5 at baseline to 27.1 at 2 months. This reduction was maintained at 6 months (26.2). The statistical significance of the decrease from baseline was not reported, but the decrease was classified as a large effect using Cohen's *d*.
Panic Disorder Severity Scale (PDSS) score	
Ostacher et al., 2021[4] High risk of bias	Mean PDSS score reduced from 9.9 at baseline to 7.5 post-treatment. This reduction was maintained at 6 months (mean score, 5.2). The statistical significance of the decrease from baseline was not reported, but the decrease was classified as a large effect using Cohen's *d*.
Clinical Global Impression – Severity Scale (CGI-S)	
Ostacher et al., 2021[4]	From baseline, mean scores on the CGI-S declined from 4.8 to 3.8 post-treatment. This reduction was maintained at 2 months (mean score, 3.0) and at 6 months (mean score, 3.0). The statistical significance of the decrease from baseline was not reported, but the decrease was classified as a large effect using Cohen's *d*.
Response, defined as a 6 point or more reduction in CAPS-5 score	
Ostacher et al., 2021[4]	In a completer analysis, 88% of participants were classed as responders at 2 months.
Remission, defined as no longer meeting *DSM-5* criteria for PTSD and having a CAPS-5 score < 25	
Ostacher et al., 2021[4]	In a completer analysis, 48% of participants were classed as responders at 2 months.

Abbreviations. CAPS-5: Clinician Administered PTSD Scale; CGI-S: Clinical Global Impression – Severity Scale; DSM-5: Diagnostic and Statistical Manual of Mental Health, Fifth Edition; NA: not applicable. NR: not reported; PDSS: Panic Disorder Severity Scale; PTSD: posttraumatic stress disorder.

Adherence

Treatment adherence was calculated by determining the proportion of Freespira sessions completed over the course of the 28-day protocol as evidenced by automatic uploads to a cloud-based server. The target number of sessions was 56. Participants completing more than 56 sessions were coded to 100% adherence.

Panic Disorder

Two studies[3,5] reported adherence to the 28-day Freespira protocol among participants with panic disorder. The average adherence was reported as 84% in both studies.

- Of 52 enrolled participants in the study by Kaplan and colleagues, 45 completed 15 or more sessions and were included in the adherence analysis. Among these 45 included in the

adherence analysis, they completed an average of 47 sessions (84% of the target 56 sessions).[3]
- No further details were reported in the study by Tolin and colleagues, other than the overall adherence of 84%.[5]

Posttraumatic Stress Disorder

One study[4] reported adherence to the 28-day Freespira protocol among participants with PTSD. The average adherence was reported as 77% in this study.

- All participants who completed 15 or more sessions were included in the adherence analysis.[4]
- No further details were reported in the study, other than the overall adherence of 77%.[4]

Quality of Life

No studies reported quality of life among participants with either panic disorder or PTSD.

Ongoing Trials

We identified 4 ongoing RCTs registered on ClinicalTrials.gov that are investigating Freespira. However, only 1 of the ongoing trials is currently still recruiting. The other 3 identified trials have been completed but do not have published results available. Registered trial characteristics are presented in Table 9.

Table 9. Characteristics of Relevant Ongoing Trials

Trial Identifier Intervention Location Completion Date Sponsor	Population Study Design Estimated Sample Size	Primary Outcomes
NCT05427708 Capnometry-Guided Respiratory Intervention US May 2025 (estimated) University of Texas Austin	Adults with anxiety or trauma-related disorders as their primary mental disorder RCT N = 180	• Change from baseline in anxiety symptoms at 2 months • Change from baseline in anxiety symptom severity at 2 months
NCT02998502 Freespira US February 2021 Johns Hopkins University	Children aged 9 to 17 years old with a prior clinical diagnosis of an anxiety disorder Crossover N = 73	• Screen for Child Anxiety-Related Disorders scale score at 8 weeks

Trial Identifier Intervention Location Completion Date Sponsor	Population Study Design Estimated Sample Size	Primary Outcomes
NCT03547180 Capnometry-Assisted Respiratory Training US March 2008 Southern Methodist University	Adults aged 18 to 65 years old with a diagnosis of panic disorder with agoraphobia RCT N = 41	• Change in panic symptom severity at 17 weeks
NCT04366011 Capnometry-Assisted Respiratory Training US October 2015 Southern Methodist University	Adults aged 18 to 65 years old with a diagnosis of panic disorder with or without agoraphobia RCT N = 40	• Panic disorder symptoms severity change at 2 months and 6 months

Abbreviations. RCT: randomized controlled trial; US: United States of America.

KQ2: Comparative Effectiveness

None of the studies directly compared the clinical effectiveness of Freespira for panic disorder versus PTSD.[3-5] Similarly, no studies explored differences in outcomes by duration or severity of panic disorder or PTSD, by comorbidities (depression, bipolar, etc.) or other readily available clinical characteristics, or by demographic characteristics. The study by Ostacher and colleagues (2021) enrolled both military veterans (N = 39) and civilians (N = 16) with PTSD but did not compare outcomes for the 2 groups.[4]

KQ3: Harms of Freespira

Serious Adverse Events

Panic Disorder

One study[5] reported adverse events while using Freespira, among 69 participants with panic disorder. No serious adverse events occurred during the study, but moderate to severe dizziness was reported in 2% of visits (6 reports from 319 participant visits) and moderate to severe lightheadedness was reported in 2% of visits (7 reports from 319 participant visits), while other adverse events (i.e., nausea, fatigue, tingling, shakiness, dry mouth) were reported in 1% of visits; however, none of the adverse events resulted in significant impairment and all ceased once the session was completed.

Posttraumatic Stress Disorder

One study[4] reported 14 adverse events while using Freespira in 55 participants with PTSD. Overall, 10 events were determined "not related" to Freespira and 4 were "possibly related" to Freespira, but none were classified as serious adverse events. Of the 4 possibly related to

Freespira, 2 occurred during active treatment (chest pain and shortness of breath). Both resolved without treatment.

Hospitalization or Emergency Department Use

No studies reported hospitalization or emergency department (ED) use among participants with either panic disorder or PTSD.

KQ4: Comparative Harms

No studies explored differences in serious adverse events, hospitalization, or emergency department use by duration or severity of panic disorder or PTSD, by comorbidities (depression, bipolar, etc.), or by demographic characteristics.

KQ5. Cost and Cost-Effectiveness

One of the identified studies included a cost-impact analysis.[3] This study used insurance claims data from the Allegheny Health Network to investigate if treatment with Freespira would significantly reduce the cost of care of panic disorder patients in the 12 months following treatment with Freespira compared to the 12 months pre-treatment. This study found that for the participants enrolled in the study (N = 52), mean overall medical costs were reduced by 35% (from $548 to $358 per member per month [PMPM]) at 12 months post-treatment. This included all medical claims for physician visits, ED visits, and diagnostic tests. The study further reported that for enrolled participants, mean ED costs were reduced by 65% (from $87 to $30 PMPM) and median pharmacy costs were reduced by 68% (from $73 to $23 PMPM) at 12 months post-treatment. However, because this study did not have a comparative control group, uncertainty remains regarding the cost-impact of treatment with Freespira. The reported results from this study may reflect the natural course of panic disorder.

KQ6. Clinical Practice Recommendations

We identified 1 publication[6] with relevant clinical practice recommendations: the VA/DoD practice guideline described below. No other recommendations or guidelines were identified that addressed use of Freespira or other biofeedback-based therapies for treatment of panic disorder or PTSD. Guidelines from the International Society for Traumatic Stress Studies, the American Psychiatric Association (APA), and the UK's National Institutes for Health and Care Excellence (NICE) focus on psychological and pharmacological treatments for PTSD and do not include references to Freespira or its predicate (Canary Breathing System), biofeedback approaches, or breathing retraining.[8-10] Similarly, guidelines from NICE do not include Freespira or Canary among 5 digitally enabled therapies that can be used as treatment options for adults with anxiety disorders,[113] and NICE guidelines on management of generalized anxiety disorder and panic disorder in adults focus solely on psychological and pharmacological interventions, without mention of biofeedback or breathing retraining approaches.[11] The Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for the treatment of panic disorder do not address biofeedback and discuss relaxation and breathing control in the context of cognitive behavioral therapy.[7] Australian guidelines advise that other approaches to breathing retraining do not have any benefit over cognitive behavioral therapy, although evidence is older and does not include any studies related to Freespira or Canary Breathing System.[7] The APA's

practice guidelines for treatment of patients with panic disorder was published in 2010, prior to the development of Freespira.[13]

VA/DoD Clinical Practice Guideline

The VA/DoD published a clinical practice guideline for the management of PTSD in 2023, and this document included a specific reference to Freespira.[6] The VA/DoD clinical practice guideline is based on a systematic review of published clinical and epidemiological evidence with the stated purpose to "provide general guidance on best evidence-based practices."[6] We assessed this clinical practice guideline as having good methodological quality. The panel that drafted the clinical practice guideline included multidisciplinary experts (i.e., internal medicine, neurology, nursing, pharmacy, psychiatry, psychology, social work and surgery).[6] The guideline panel did not include any patients, but they considered feedback from a patient focus group while drafting the guideline.

Key findings and recommendations related to the treatment of PTSD with Freespira was limited to the following: "There is insufficient evidence to recommend for or against the following somatic therapies for the treatment of PTSD: capnometry-assisted respiratory therapy (Freespira)."[6]

KQ7. Payer Policies

We identified coverage policies that mentioned Freespira from 4 of the 13 private payers and 1 of the 10 Medicaid programs searched for this report: Aetna, Anthem Blue Cross and Blue Shield (formerly Empire BlueCross BlueShield), Highmark Inc., Molina Healthcare, and the Medicaid program in Oregon (Oregon Health Plan).[14-17,19,20] We identified coverage policies on biofeedback from CMS, 5 of the 13 private payers, and 7 of the 10 Medicaid programs searched for this report: Aetna; Anthem Blue Cross and Blue Shield (formerly Empire BlueCross BlueShield); Cigna Healthcare; Excellus BlueCross BlueShield; Highmark Inc.; and the Medicaid programs in California (Medi-Cal), Massachusetts (MassHealth), New Jersey (NJ FamilyCare), New York, Oregon (Oregon Health Plan), Texas, and Washington State (Apple Health).[24-35,37-40,114] See Table 10 for a summary of coverage decisions from the policies and Appendix I for a full description of the policies. See Appendix A for the policy sources searched and terms used to identify relevant coverage policies.

Among the 5 payers that had policies that mentioned Freespira, 1 payer had partnered with the manufacturer to cover this digital therapeutic biofeedback device (Highmark Inc.).[33] Highmark Inc.'s policy on biofeedback indicated that capnometry-guided respiratory intervention (in the policy, Freespira was provided as an example of this type of biofeedback) may be considered medically necessary as part of an overall treatment plan for individuals aged 18 years and older who are diagnosed with panic disorder or PTSD.[33] The policy specified that individuals must be physically and cognitively capable of participating in a treatment plan utilizing capnometry guided respiratory intervention.[33] Freespira was available to Highmark Inc. commercial and Affordable Care Act members in Delaware, Pennsylvania, and West Virginia.[17] One of the studies[3] included in the clinical evidence review reported the results of a quality improvement program conducted through a Highmark Health initiative to make new technologies and services not yet covered by commercial insurers available to patients.[21] Highmark Health is a blended health organization that includes health insurance plans (e.g., Highmark Blue Shield of

Northeastern New York), health care delivery (e.g., Allegheny Health Network), and health technology firms (e.g., enGen, Helion).[23] The authors of the included study worked for the Allegheny Health Network and recruited patients within this network who had health insurance coverage from Highmark Blue Cross Blue Shield (a subsidiary of Highmark Inc. that provides health insurance for individuals in western, north central, and northeastern Pennsylvania).[3,23]

The 4 payers that did not cover Freespira considered the product experimental, investigational, and unproven.[14-16,19,20,115] Two policies (Aetna and the Behavioral Health Advisory Panel for Oregon's Health Evidence Review Commission [HERC]) stated that there was insufficient evidence to establish the effectiveness of Freespira.[15,19,20,115] Three policies (Anthem Blue Cross and Blue Shield, Molina Healthcare, and the Behavioral Health Advisory Panel for Oregon's HERC) noted concerns about the available studies, including small sample size, lack of comparison to accepted standards of medical practice (e.g., behavioral therapy, pharmaceutical therapy), and a high loss to follow-up.[14,16,19,20,115]

One of the 13 payers that had policies on biofeedback covered this service for patients with panic disorder or PTSD (Highmark Inc.; see Table 10).[17,33] As noted earlier, Highmark Inc.'s biofeedback policy indicated that capnometry-guided respiratory intervention (with Freespira provided as an example of this type of biofeedback) may be considered medically necessary as part of an overall treatment plan for individuals aged 18 years and older who are diagnosed with panic disorder or PTSD, and is available to members in Delaware, Pennsylvania, and West Virginia.[17,33] Biofeedback services were on the New York State Department of Health list of never pay procedures under ambulatory patient group reimbursement, with no alternative payment methods available.[35]

The national coverage determination (NCD) on biofeedback therapy indicated that Medicare covers biofeedback therapy for patients who require retraining of specific muscle groups or treatment of muscle weakness or spasticity when conventional treatments have failed.[27] Medicare also covers biofeedback services, provided by a practitioner in an office or other facility setting, for patients with urinary incontinence who have failed pelvic muscle exercise training.[26] The NCD stated that Medicare does not cover biofeedback therapy for treatment of muscle tension or psychosomatic conditions, nor does it cover home use of biofeedback therapy.[26,27]

Two policies (Aetna and Anthem Blue Cross and Blue Shield) indicated that biofeedback was considered investigational for panic disorder and PTSD.[29,30] In October 2020, the Behavioral Health Advisory Panel for Oregon's HERC found no evidence supporting the use of biofeedback for treatment of mental health conditions.[36] The panel recommended that biofeedback not be added to any behavioral health conditions on the Prioritized List of Health Services.[36] Biofeedback and neurofeedback for children with a history of trauma was discussed at the November 2022 HERC meeting.[37] Staff noted that no new evidence had emerged regarding the efficacy of biofeedback or neurofeedback for PTSD or children with a history of trauma and recommended no changes to their policy not to cover these services for PTSD or related conditions.[37] At present, Oregon Health Plan covers biofeedback services (CPT codes 90901, 90875, and 90876; see Table J1 for a description of these codes) for patients with migraine or tension headaches or when provided as palliative care for treatment of cancer pain.[114]

Four private payer policies (Aetna, Anthem Blue Cross and Blue Shield, Cigna Healthcare, and Excellus BlueCross BlueShield) stated that use of in-home biofeedback devices was considered investigational (with the exception that Cigna Healthcare covered the Leva Pelvic Health System in-home device and remotely delivered program for urinary incontinence).[29-32] Texas Medicaid, which covers biofeedback services for individuals aged 4 years and older with urinary incontinence, fecal incontinence, or migraine or tension headache, specified that biofeedback performed in the home setting or as part of psychological, psychophysiological, or behavioral health therapy is not a benefit.[38,39]

Table 10. Summary of Coverage for Freespira and Biofeedback

Payer	Freespira Covered? Last Review Date	Biofeedback Covered for Patients With Panic Disorder or PTSD? Last Review Date
Private payers		
Aetna	**No** July 17, 2024[15]	**No** October 11, 2024[29]
Anthem Blue Cross Blue Shield	**No** August 8, 2024[14]	**No** May 9, 2024[30]
Capital District Physicians' Health Plan	No policy identified	No policy identified
Cigna Healthcare	No policy identified	**No** November 15, 2023[31]
EmblemHealth	No policy identified	No policy identified
Excellus BlueCross BlueShield	No policy identified	**No** June 20, 2024[32]
Fidelis Care	No policy identified	No policy identified
Healthfirst	No policy identified	No policy identified
Highmark Inc[a]	**Yes** No month provided 2024[17]	**Yes** April 2024[33]
MetroPlusHealth	No policy identified	No policy identified
Molina Healthcare	**No** April 10, 2024[16]	No policy identified
Tufts Health Plan	No policy identified	No policy identified
UnitedHealthcare	No policy identified	No policy identified
Medicare		
Centers for Medicare & Medicaid Services	No policy identified	**No** No effective date posted[27]

Payer	Freespira Covered? Last Review Date	Biofeedback Covered for Patients With Panic Disorder or PTSD? Last Review Date
		July 1, 2022[26]
State Medicaid programs		
California (Medi-Cal)	No policy identified	**No** October 2024[25]
Florida	No policy identified	No policy identified
Massachusetts (MassHealth)	No policy identified	**No** August 1, 2024[34]
New Jersey (NJ FamilyCare)	No policy identified	**No** December 5, 2022[24,28]
New York	No policy identified	**No** January 1, 2024[35]
North Carolina	No policy identified	No policy identified
Oregon (Oregon Health Plan)	**No** June 28, 2023[19] August 17, 2023[20]	**No** October 21, 2020[36] November 17, 2022[37] October 1, 2024[114]
Pennsylvania	No policy identified	No policy identified
Texas	No policy identified	**No** October 2024[38,39]
Washington state (Apple Health)	No policy identified	**No** October 1, 2024[40] October 9, 2024[41]

Note. [a] Freespira is available to Highmark Inc. commercial and Affordable Care Act members in Delaware, Pennsylvania, and West Virginia.
Abbreviation. PTSD: posttraumatic stress disorder.

Discussion

While Freespira is reported to improve symptoms related to PTSD or panic disorder, it is not associated with serious adverse events, and the majority of patients are adherent to the 28-day Freespira treatment protocol, we have very low certainty in these findings.[3-5] Evidence related to Freespira is limited to 3 small, non-comparative studies: 2 in adults with panic disorder and 1 in adults with PTSD. When designing the protocol for this review, non-comparative study designs were only included because of a lack of published higher-level evidence (i.e., RCTs). The limited number of trials, lack of control groups, small sample sizes, high attrition rates, and overall high-risk of bias should be considered when drawing conclusions about the certainty of evidence for Freespira for the treatment of panic disorder and PTSD. The uncertainty in the validity of the reported outcomes is further compounded by lack of clear and consistent data reporting within

the publications. Overall, we have very low certainty in these results, and new research is likely to change our understanding of Freespira for panic disorder and PTSD.

A single cost analysis for Freespira suggested that the treatment reduced the cost of care of panic disorder patients.[3] The study found that overall medical costs, ED costs, and pharmacy costs were reduced in the 12 months post-treatment with Freespira compared to the 12 months pre-treatment.[3] Again, however, this is based on a single small pre-post study in a single health care system, limiting our ability to draw robust conclusions on the impact of Freespira use on health care spending more generally. The decrease in spending after the intervention may simply represent the natural history of the condition or the effects of other types of treatment.

The VA/DoD clinical practice guideline for the management of PTSD (2023) included Freespira in a section related to non-pharmacological biological treatments for improving PTSD symptoms but concluded that there was insufficient evidence to recommend for or against Freespira or other somatic treatments.[6] Other identified guidelines and recommendations for treatment of panic disorder or PTSD focused on psychological and pharmacological approaches to treatment and do not address Freespira, biofeedback-based approaches to treatment, or breathing retraining.[7-13]

There are currently no federal requirements for coverage of prescription digital therapeutics by Medicaid. One of the 5 coverage policies related to Freespira covered this product.[33] The 4 payers that did not cover Freespira considered the product experimental, investigational, and unproven.[14-16,19,20,115] One of the 13 coverage policies on biofeedback covered this service for patients with panic disorder or PTSD.[33] Biofeedback was on the New York State Department of Health list of never pay procedures under ambulatory patient group reimbursement.[35]

In summary, we conclude that based on the information included in this report there is very low certainty of evidence on the effectiveness and safety of Freespira for panic disorder and PTSD. The majority of payers we surveyed do not cover Freespira.

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Appendix A. Search Methods

Clinical Evidence Sources and Search Strategies

We searched selected bibliographic databases and grey literature sources using key words such as *digital therapeutic*, *post-traumatic stress disorder*, *panic disorder*, *agoraphobia*, *Freespira*, *Canary breathing system*, and *capnometry* to identify randomized controlled trials, nonrandomized comparative trials, prospective cohort studies, before-after studies, cost and cost-effectiveness studies, and clinical practice guidelines. We did not use date limits, but we did limit search results to publications available in the English language. Searches were conducted February 21 through 26, 2024.

Bibliographic Database Sources

- Cochrane Central Register of Controlled Trials (CENTRAL)
- Cochrane Database of Systematic Reviews (CDSR)
- PTSDpubs (formerly PILOTS)
- Ovid MEDLINE
- Ovid PsycInfo

Evidence Synthesis Sources

- Agency for Healthcare Research and Quality (AHRQ)
- Canada's Drug Agency
- Epistemonikos
- Health Quality Ontario
- Institute for Clinical and Economic Review (ICER)
- Institute for Health Quality and Efficiency in Health Care (IQWiG)
- International HTA Database
- National Institute for Health and Care Excellence (NICE)
- Oregon Health Evidence Review Commission (HERC)
- Veterans Administration Evidence Synthesis Program
- Washington Health Technology Assessment

Clinical Practice Guideline Sources

- American Medical Association (AMA)
- American Psychiatric Association
- American Psychological Association
- Anxiety and Depression Association of America
- Association for Psychological Science
- Canadian Medical Association
- Guidelines International Network (GIN) International Guidelines Library
- International Society for Traumatic Stress Studies
- National Center for PTSD
- National Institute for Health and Care Excellence (NICE)
- Scottish Intercollegiate Guidelines Network (SIGN)
- US Preventive Services Task Force
- Veterans Administration/Department of Defense Clinical Practice Guidelines
- World Psychiatric Association

Clinical Trial Sources

- ClinicalTrials.gov
- ScanMedicine

Regulatory Body and Manufacturer Sources

- US Food and Drug Administration Devices@FDA
- US Food and Drug Administration Manufacturer and User Facility Device Experience (MAUDE)

Ovid MEDLINE ALL Search Strategy

1	exp stress disorders, traumatic/
2	panic disorder/
3	agoraphobia/
4	((post-trauma* or post trauma* or posttrauma*) adj3 (disorder* or neuros* or psych* or stress* or symptom*)).ti,ab,kw.
5	acute stress disorder*.ti,ab,kw.
6	combat disorder*.ti,ab,kw.
7	war neuros*.ti,ab,kw.
8	ptsd.ti,ab,kf.
9	desnos.ti,ab,kf.
10	(panic adj3 (attack* or disorder*)).ti,ab,kw.
11	agoraphob*.ti,ab,kf.
12	(open space? adj3 (fear* or phob*)).ti,ab,kw.
13	or/1-12
14	breathing exercises/
15	biofeedback, psychology/
16	capnography/
17	(free-spira or free spira or freespira).ti,ab,kw.
18	(canary adj3 breath*).ti,ab,kw.
19	capnograph*.ti,ab,kf.
20	capnomet*.ti,ab,kf.
21	cgri.ti,ab,kf.
22	((carbon dioxide or co2 or co-2 or co 2) adj3 (assist* or end-tidal or end tidal or endtidal or guide*)).ti,ab,kw.
23	digital therap*.ti,ab,kw.
24	or/14-23
25	clinical decision rules/
26	consensus/
27	exp consensus development conferences as topic/
28	critical pathways/
29	decision making, shared/
30	exp guidelines as topic/
31	health planning guidelines/
32	consensus development conference.pt.

33 consensus development conference, NIH.pt.
34 guideline.pt.
35 practice guideline.pt.
36 consensus.ti,kf.
37 guideline?.ti,kf.
38 position*.ti,kf.
39 recommend*.ti,kf.
40 ((committee or executive) adj2 (statement or summary)).ti,kw.
41 ((joint or position) adj2 statement).ti,kw.
42 ((clinical or critical or practice) adj2 (path* or pathway or standard? or statement)).ti,kw.
43 or/25-42
44 and/13,24
45 exp animals/ not humans/
46 44 not 45
47 and/13,43
48 limit 47 to yr="2019 -Current"
49 or/46,48
50 limit 49 to english language

Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Trials via the Cochrane Library

1 [mh "stress disorders, traumatic"]
2 [mh ^"panic disorder"]
3 [mh ^agoraphobia]
4 (((post-trauma* OR "post trauma" OR posttrauma) NEAR/3 (disorder* OR neuros* OR psych* OR stress* OR symptom*))):ti,ab,kw
5 ("acute stress" NEXT disorder*):ti,ab,kw
6 (combat NEXT disorder*):ti,ab,kw
7 (war NEXT neuros*):ti,ab,kw
8 ptsd:ti,ab,kw
9 desnos:ti,ab,kw
10 (panic NEAR/3 (attack* OR disorder*)):ti,ab,kw
11 agoraphob*:ti,ab,kw
12 ((open NEXT space?) NEAR/3 (fear* OR phob*)):ti,ab,kw
13 [OR #1-#12]
14 [mh ^"breathing exercises"]
15 [mh ^"biofeedback, psychology"]
16 [mh ^capnography]
17 (free-spira OR "free spira" OR freespira):ti,ab,kw
18 (canary NEAR/3 breath*):ti,ab,kw
19 capnograph*:ti,ab,kw
20 capnomet*:ti,ab,kw

21 cgri:ti,ab,kw
22 (("carbon dioxide" OR co2 OR co-2 OR "co 2") NEAR/3 (assist* OR end-tidal OR "end tidal" OR endtidal OR guide*)):ti,ab,kw
23 ("digital" NEXT therap*,kw.):ti,ab
24 [OR #14-#23]
25 [AND #13, #24]

PsycInfo

1 exp posttraumatic stress disorder/
2 posttraumatic stress/
3 acute stress disorder/
4 traumatic neurosis/
5 panic attack/
6 panic disorder/
7 agoraphobia/
8 ((post-trauma* or post trauma* or posttrauma*) adj3 (disorder* or neuros* or psych* or stress* or symptom*)).ti,ab,id.
9 acute stress disorder*.ti,ab,id.
10 combat disorder*.ti,ab,id.
11 war neuros*.ti,ab,id.
12 ptsd.ti,ab,id.
13 desnos.ti,ab,id.
14 (panic adj3 (attack* or disorder*)).ti,ab,id.
15 agoraphob*.ti,ab,id.
16 (open space? adj3 (fear* or phob*)).ti,ab,id.
17 or/1-16
18 biofeedback/
19 biofeedback training/
20 (free-spira or free spira or freespira).ti,ab,id.
21 (canary adj3 breath*).ti,ab,id.
22 capnograph*.ti,ab,id.
23 capnomet*.ti,ab,id.
24 cgri.ti,ab,id.
25 ((carbon dioxide or co2 or co-2 or co 2) adj3 (assist* or end-tidal or end tidal or endtidal or guide*)).ti,ab,id.
26 digital therap*.ti,ab,id.
27 or/18-26
28 and/17,27
29 limit 28 to english language
30 limit 29 to ("0100 journal" or "0110 peer-reviewed journal" or "0120 non-peer-reviewed journal" or "0130 peer-reviewed status unknown" or "0500 electronic collection")

PTSDpubs

S1	MAINSUBJECT.EXACT.EXPLODE("PTSD")
S2	MAINSUBJECT.EXACT("Acute Stress Disorder")
S3	MAINSUBJECT.EXACT.EXPLODE("Traumatic Neuroses")
S4	MAINSUBJECT.EXACT("Panic Disorder")
S5	TITLE(((post-trauma* OR "post trauma" OR posttrauma) NEAR/3 (disorder* OR neuros* OR psych* OR stress* OR symptom*))) OR ABSTRACT(((post-trauma* OR "post trauma" OR posttrauma) NEAR/3 (disorder* OR neuros* OR psych* OR stress* OR symptom*))) OR IF(((post-trauma* OR "post trauma" OR posttrauma) NEAR/3 (disorder* OR neuros* OR psych* OR stress* OR symptom*)))
S6	TITLE("acute stress disorder*") OR ABSTRACT("acute stress disorder*") OR IF("acute stress disorder*")
S7	TITLE("combat disorder*") OR ABSTRACT("combat disorder*") OR IF("combat disorder*")
S8	[STRICT] TITLE("war neuros*") OR ABSTRACT("war neuros*") OR IF("war neuros*")
S9	TITLE(ptsd) OR ABSTRACT(ptsd) OR IF(ptsd)
S10	TITLE(desnos) OR ABSTRACT(desnos) OR IF(desnos)
S11	TITLE(panic NEAR/3 (attack* OR disorder*)) OR ABSTRACT(panic NEAR/3 (attack* OR disorder*)) OR IF(panic NEAR/3 (attack* OR disorder*))
S12	TITLE(agoraphob*) OR ABSTRACT(agoraphob*) OR IF(agoraphob*)
S13	TITLE("open space?" NEAR/3 (fear* OR phob*)) OR ABSTRACT("open space?" NEAR/3 (fear* OR phob*)) OR IF("open space?" NEAR/3 (fear* OR phob*))
S14	[S1] OR [S2] OR [S3] OR [S4] OR [S5] OR [S6] OR [S7] OR [S8] OR [S9] OR [S10] OR [S11] OR [S12] OR [S13]
S15	MAINSUBJECT.EXACT("Biofeedback Training")
S16	TITLE(free-spira OR "free spira" OR freespira) OR ABSTRACT(free-spira OR "free spira" OR freespira) OR IF(free-spira OR "free spira" OR freespira)
S17	TITLE(canary NEAR/3 breath*) OR ABSTRACT(canary NEAR/3 breath*) OR IF(canary NEAR/3 breath*)
S18	TITLE(capnograph*) OR ABSTRACT(capnograph*) OR IF(capnograph*)
S19	TITLE(capnomet*) OR ABSTRACT(capnomet*) OR IF(capnomet*)
S20	TITLE(cgri) OR ABSTRACT(cgri) OR IF(cgri)
S21	TITLE((("carbon dioxide" OR co2 OR co-2 OR "co 2") NEAR/3 (assist* OR end-tidal OR "end tidal" OR endtidal OR guide*))) OR ABSTRACT((("carbon dioxide" OR co2 OR co-2 OR "co 2") NEAR/3 (assist* OR end-tidal OR "end tidal" OR endtidal OR guide*))) OR IF((("carbon dioxide" OR co2 OR co-2 OR "co 2") NEAR/3 (assist* OR end-tidal OR "end tidal" OR endtidal OR guide*)))
S22	[S16] OR [S17] OR [S18] OR [S19] OR [S20] OR [S21] OR [S22]
S23	[S14] AND [S22]
S24	[S14] AND [S22] AND stype.exact("Scholarly Journals" OR "Reports")

Policy Sources and Search Terms

We searched websites for the state Medicaid programs and private payers listed below using terms such as *digital therapeutic*, *mobile app*, *biofeedback*, and *Freespira*.

State Medicaid Programs

- California Medicaid
- Florida Medicaid
- Massachusetts Medicaid
- New Jersey Medicaid
- New York Medicaid
- North Carolina Medicaid
- Oregon Medicaid and the Health Evidence Review Commission (HERC) coverage guidance (including topics under consideration)
- Pennsylvania Medicaid
- Texas Medicaid
- Washington Medicaid and the Washington Health Technology Assessment Program coverage determinations (including topics under consideration)

Private Payers

- Aetna
- Anthem Blue Cross and Blue Shield (formerly Empire BlueCross BlueShield)
- Capital District Physicians' Health Plan
- Cigna Healthcare
- EmblemHealth
- Excellus BlueCross BlueShield
- Fidelis Care
- Healthfirst
- Highmark Inc.
- MetroPlusHealth
- Molina Healthcare
- Tufts Health Plan
- UnitedHealthcare

Appendix B. Detailed Inclusion and Exclusion Criteria

Table B. Detailed Inclusion and Exclusion Criteria

Study Component	Inclusion	Exclusion
Populations	• Individuals aged 18 years or older diagnosed with 1 or more of the following: o Panic disorder without agoraphobia o Panic disorder with agoraphobia o PTSD	• Individuals less than 18 years of age • Individuals not meeting the included diagnoses
Interventions	• Freespira (capnometry-guided respiratory intervention) prescription digital therapeutic, with or without standard interventions (e.g., psychotherapy, pharmacotherapy)	• For KQs 1 through 3, other prescription digital therapeutics intended to manage panic disorder or PTSD
Comparators	• Head-to-head comparisons with other prescription digital therapeutics • Standard care (e.g., pharmacotherapy, psychotherapy) • No comparison group	• None listed
Outcomes	<u>Critical</u> • Symptoms related to panic disorder or PTSD, assessed by validated measures, such as: o Panic Disorder Severity Scale (PDSS) o Sheehan Disability Scale (SDS) o Clinical Global Impression – Severity Scale (CGI-S) o Beck Depression Inventory (BDI) o Anxiety Sensitivity Index (ASI) o Clinician Administered PTSD Scale (CAPS-5) • Treatment adherence, measured as number of completed sessions in 28 -day protocol <u>Important</u> • Patient-reported quality of life • Hospitalization or emergency department use related to panic disorder or PTSD • Serious adverse events	• Respiratory rate • End-tidal carbon dioxide
Timing and follow-up	• Minimum follow-up of 1 month after the end of the intervention period	• Less than 1 month of follow-up after the end of the intervention period
Setting	• Studies conducted in outpatient settings • Studies conducted in countries categorized as *very high* on the Human Development Index	• Sessions conducted in inpatient setting • Studies conducted in countries not categorized as *very high* on the Human Development Index

Study Component	Inclusion	Exclusion
Study design	KQ1–KQ2 • Randomized controlled trials • Nonrandomized comparative trials • Prospective cohort studies • Interrupted time series with comparison group • Controlled before-after studies • Uncontrolled before-after studies KQ3 • Comparative studies and economic evaluations • Cost-effectiveness analyses • Economic modeling studies KQ4 • Evidence-based clinical practice guidelines that provide specific treatment recommendations	• Studies without extractable data • Retrospective studies unless otherwise noted
Sample size	• No limit	• None listed
Publication type	• Peer-reviewed publication of primary study results • Published in the English language • Ancillary publications with additional comparative follow-up	• Abstracts, conference proceedings, posters, editorials, letters • Studies that have not been formally peer reviewed (i.e., preprint publications) • Studies published in languages other than English • Studies that cannot be found • Duplicate publications of the same study that do not report different outcomes or follow-up times, or single-site reports from published multicenter studies

Abbreviations. KQ: key question; PTSD: posttraumatic stress disorder.

Appendix C. Additional Methods

Table C1. Risk of Bias Assessment: Nonrandomized Studies

Domain	Domain Elements[a]
Participant selection	For cohort studies: • The 2 groups being studied are selected from source populations comparable in all respects other than factor under investigation, or statistical adjustment is used appropriately to achieve this • The study indicates how many of people asked to take part did so in each of the groups being studied • The likelihood some eligible participants might have outcome at time of enrollment is assessed and considered in analysis • Fewer than 20% of individuals or clusters in each arm of study dropped out before study was completed For case-control studies: • Cases and controls are clearly specified and defined, with inclusion and exclusion criteria applied appropriately • Cases may be selected by meeting inclusion criteria, controls may be selected by meeting inclusion criteria and then being matched to cases • Sampling selection (ratio of cases to control) is justified • Cases and controls selected from same population and same timeframe; when not all cases and controls are selected from same population, these are randomly selected • Among cases, investigators confirm that exposure occurred before development of disease being studied and/or likelihood that some eligible participants might have outcome at time of enrollment is assessed and considered in analysis
Intervention	• The assessment of exposure to intervention is reliable • Exposure level or prognostic factors are assessed at multiple times across length of study, if appropriate • For case-control studies, assessors of (intervention) exposure status are unaware (masked or blinded) to case or control status of participants, and there is a method to limit effects of recall bias on assessment of exposure to intervention
Control	• Control condition represents an appropriate comparator
Outcome	• There is a precise definition of outcomes used • Outcomes are measured using valid and reliable measures, evidence from other sources is used to demonstrate method of outcome assessment is valid and reliable • Investigators use single outcome measures and do not rely on composite outcomes, or outcome of interest can be calculated from composite outcome • The study has an appropriate length of follow-up for outcome reported and groups are assessed at same time points • Outcome reporting of entire group or subgroups is not selective • When patient-reported outcomes are used, there is a method for validating measure
Masked outcome assessment	• The assessment of outcome(s) is made blind to exposure status. Where outcome assessment blinding was not possible, there is recognition that knowledge of exposure status could have influenced assessment of outcome. • For case-control study: assessors of exposure status are unaware (masked or blinded) of case or control status of participant

Domain	Domain Elements[a]
Confounding	• The main potential confounders are identified and considered in design and analysis of study
Statistical analysis	• Comparison is made between full participants and those who dropped out or were lost to follow-up, by exposure status • If groups were not followed for an equal length of time, analysis was adjusted for differences in length of follow-up • All major confounders are adjusted for using multiple variable logistic regression or other appropriate statistical methods • Confidence intervals (or information used to calculate them) are provided • For case-control studies that use matching, conditional analysis is conducted or matching factors are adjusted for in analysis
Other biases (as appropriate)	• List others in table footnote and describe • Sample size adequacy
Interest disclosure	• Disclosures of interest are provided for authors/funders/commissioners of study • Interests are unlikely to significantly affect study validity
Funding source	• There is a description of source(s) of funding • Funding source is unlikely to have a significant impact on study validity

Note. [a] The elements included in each domain are assessed and rated as yes, no, unclear, or not applicable based on performance and documentation of individual elements in each domain. The overall risk of bias for a study is assessed as high, moderate, or low based on assessment of how well overall study methods and processes were performed to limit bias and ensure validity.

Table C2. Methodological Quality Assessment: Clinical Practice Guidelines

Domain	Domain Elements[a]
Rigor of development: evidence	• Systematic literature search meets quality standards for a systematic review (i.e., comprehensive search strategy with, at a minimum, 2 or more electronic databases) • The criteria used to select evidence for inclusion is clear and appropriate • The strengths and limitations of individual evidence sources is assessed and overall quality of body of evidence assessed
Rigor of development: recommendations	• Methods for developing recommendations clearly described and appropriate • There is an explicit link between recommendations and supporting evidence • The balance of benefits and harms is considered in formulating recommendations • The guideline has been reviewed by external expert peer reviewers • The updating procedure for guideline is specified in guideline or related materials (e.g., specialty society website)
Editorial independence	• There is a description of source(s) of funding and views of funder(s) are unlikely to have influenced content or validity of guideline • Disclosures of interests for guideline panel members are provided and are unlikely to have a significant impact on overall validity of guideline (e.g., a process for members to recuse themselves from participating on recommendations for which a significant conflict is provided)
Scope and purpose	• Objectives specifically described • Health question(s) specifically described • Target population(s) for guideline recommendations is specified (e.g., patients in primary care) and target users for guideline (e.g., primary care clinicians)

Domain	Domain Elements[a]
Stakeholder involvement	• Relevant professional groups represented • Views and preferences of target population(s) sought (e.g., clinicians and patients)
Clarity and presentation	• Recommendations are specific and unambiguous • Different management options are clearly presented • Key recommendations are easily identifiable
Applicability	• Provides advice and/or tools on how recommendation(s) can be put into practice • Description of facilitators and barriers to its application • Potential resource implications considered • Criteria for implementation monitoring, audit, and/or performance measures based on guideline are presented

Note. [a] *The elements included in each domain are assessed and rated as* yes, no, unclear, *or* not applicable *based on performance and documentation of individual elements in each domain. The overall risk of bias for a study is assessed as* high, moderate, *or* low *based on assessment of how well overall study methods and processes were performed to limit bias and ensure validity.*

Table C3. GRADE System for Rating the Certainty of Evidence for Outcomes

GRADE Rating	Plain Language Description	Detailed Category Description
High	New research is very unlikely to change our understanding of the relationship between this outcome and the health technology.	Center researchers are very confident that the estimate of the effect of the intervention on the outcome lies close to the true effect. Typical sets of studies are RCTs with few or no limitations, and the estimate of effect is likely stable.
Moderate	New research may change our understanding of the relationship between this outcome and the health technology.	Center researchers are moderately confident in the estimate of the effect of the intervention on the outcome. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is different. Typical sets of studies are RCTs with some limitations or well-performed nonrandomized studies with additional strengths that guard against potential bias and have large estimates of effects.
Low	New research is likely to change our understanding of the relationship between this outcome and the health technology.	Center researchers have little confidence in the estimate of the effect of the intervention on the outcome. The true effect may be substantially different from the estimate of the effect. Typical sets of studies are RCTs with serious limitations or nonrandomized studies without special strengths.
Very low	New research is very likely to change our understanding of the relationship between this outcome and the health technology.	Center researchers have no confidence in the estimate of the effect of the intervention on the outcome. The true effect is likely to be substantially different from the estimate of effect. Typical sets of studies are nonrandomized studies with serious limitations or inconsistent results across studies.
Not applicable	There is no research to report.	Center researchers did not identify any eligible articles.

Source. Adapted from 2 publications about GRADE.[116,117]

Abbreviations. GRADE: Grading of Recommendations, Assessment, Development, and Evaluations; RCT: randomized controlled trial.

Appendix D. Included Studies

Table D. Included Studies

Primary Publication From Included Trial	Publications Reporting Additional Results
Kaplan et al. 2020[3] Alleghany Health Network, Quality Improvement Program	None
Ostacher et al. 2021[4] NCT03039231	None
Tolin et al. 2017[5] NCT01955954	Davies et al. (2019)[118] conducted post hoc multilevel mediation analyses on this clinical trial to examine the mediation effects of different variables on panic symptom change. However, as this did not report on the direct effect of Freespira use, we did not include it in this review.

Appendix E. Risk of Bias/Methodological Quality Assessment

Table E1. Risk of Bias: Nonrandomized Studies

Study	Study Design has a Control Group	Generalizability	Overall Risk of Bias[a]
Kaplan et al. 2020	No control group	Yes	High
Ostacher et al. 2021	No control group	Yes	High
Tolin et al. 2017	No control group	Yes	High

Note. [a] Any study without a comparator is automatically considered to be at high risk of bias.

Table E2. Methodological Quality Assessment: Clinical Practice Guidelines

Publication	Rigor of Development: Evidence	Rigor of Development: Recommendations	Editorial Independence	Scope and Purpose	Stakeholder Involvement	Clarity and Presentation	Applicability	Overall Methodological Quality
2023 VA/DoD Clinical Practice Guideline	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good

Abbreviations. DoD: Department of Defense; VA: Department of Veterans Affairs.

Appendix F. GRADE Assessment

Table F. GRADE Profile: Freespira for PTSD and Panic Disorder

Outcome	Number of Participants and Studies	Study Design(s)	Factors That May Decrease Certainty of Evidence					Relationship	Certainty of Evidence
			Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias		
Symptom reduction	3 studies N = 176	Single-arm cohort studies	Very serious (-2) See Risk of Bias assessment	No serious	No serious	Serious imprecision (-1), small sample sizes	Not assessed	Freespira was associated with statistically significant and clinically meaningful improvement in both panic disorder and PTSD symptoms, relative to patient baseline, which were maintained at 12 months. However, without a control group, we cannot be certain if this effect was associated directly with Freespira use or reflective of the natural course of panic disorder and PTSD over time.	●○○○ VERY LOW

Outcome	Number of Participants and Studies	Study Design(s)	Factors That May Decrease Certainty of Evidence					Relationship	Certainty of Evidence
			Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias		
Adherence	3 studies N = 176	Single-arm cohort studies	Very serious (-2) See Risk of Bias assessment	No serious	No serious	Serious imprecision (-1), small sample sizes	Not assessed	Freespira was associated with a high level of adherence (around 77% to 84%).	●○○○ VERY LOW
Serious adverse events	2 studies N = 124	Single-arm cohort studies	Very serious (-2) See Risk of Bias assessment	No serious	No serious	Serious imprecision (-1), small sample sizes	Not assessed	There were no reports of serious adverse events with Freespira use.	●○○○ VERY LOW
Hospitalization or ED use	Not reported								NA
Quality of life	Not reported								NA

Abbreviations. ED: emergency department; NA: not applicable; PTSD: posttraumatic stress disorder.

Appendix G. Additional Evidence Tables

Table G1. Change in Panic Disorder Symptoms

Author, Year Risk of Bias	Baseline N Mean (SD)	Post-treatment N Mean (SD)	Month-6 N Mean (SD)	Month-12 N Mean (SD)
Panic Disorder Severity Scale Score				
Kaplan et al., 2020[3] High risk of bias	N = 50 Mean, 14.4 (3.8)	N = 44 Mean, 4.9 (3.4) 66% decrease from baseline (*P* < .01)	N = 27 Mean, 4.1 (4.3) 72% decrease from baseline (*P* < .01)	N = 22 Mean, 4.4 (4.5) 69% decrease from baseline (*P* < .01)
Tolin et al., 2017[5] High risk of bias	N = 69 Mean, 14.8 (3.6)	N = 53 Mean, 5.4 (4.4)	N = 42 Mean, NR	N = 33 Mean, 5.0 (6.2)
Sheehan Disability Scale				
Kaplan et al., 2020[3] High risk of bias	N = 50 Mean, 14.7 (6.5)	N = 44 Mean, 5.9 (5.0)	N = 27 Mean, 3.8 (5.8)	N = 22 Mean, 5.0 (5.6)
Tolin et al., 2017[5] High risk of bias	N = 69 Mean, 14.4 (6.7)	N = 53 Mean, 7.4 (6.7)	N = 42 Mean, NR	N = 33 Mean, 6.1 (6.6)
Clinical Global Impression – Severity scale				
Kaplan et al., 2020[3] High risk of bias	N = 50 Mean, 4.4 (0.7)	N = 44 Mean, 2.8 (0.8)	N = 27 Mean, 2.1 (1.0)	N = 22 Mean, 2.1 (0.9)
Tolin et al., 2017[5] High risk of bias	N = 69 Mean, 4.5 (0.7)	N = 53 Mean, 2.7 (1.0)	N = 42 Mean, NR	N = 33 Mean, 2.1 (1.1)
% Participants with ≥ 40% Panic Disorder Severity Score reduction (responders)				
Kaplan et al., 2020[3] High risk of bias	N = 50 N/A	N = 44 66%	N = 27 72%	N = 22 69%
Tolin et al., 2017[5] High risk of bias	N = 69 N/A	N = 53 85%	N = 42 NR	N = 33 82%
% Participants with Panic Disorder Severity Score ≤ 5 (remission)				
Kaplan et al., 2020[3] High risk of bias	N = 50 N/A	N = 44 82%	N = 27 85%	N = 22 91%
Tolin et al., 2017[5] High risk of bias	N = 69 N/A	N = 53 56%	N = 42 NR	N = 33 70%

Abbreviation. NA: not applicable. NR: not reported.

Table G2. Change in Posttraumatic Stress Disorder Symptoms

Author, Year Risk of Bias	Baseline N Mean (SD)	Post-treatment N Mean (SD)	Month-2 N Mean (SD)	Month-6 N Mean (SD)
Panic Disorder Severity Scale Score				
Ostacher et al., 2021[4] High risk of bias	N = 55 Mean, 9.9 (5.4)	N = 48 Mean, 7.5 (6.4)	N = 42 Mean, 6.0 (6.4)	N = 38 Mean, 5.2 (7.3)
Clinician Administered PTSD Scale (CAPS-5)				
Ostacher et al., 2021[4] High risk of bias	N = 55 Mean, 49.5 (9.2)	N = 48 Mean, 31.8 (14.1)	N = 42 Mean, 27.1 (17.8)	N = 38 Mean, 26.2 (18.4)
Clinical Global Impression – Severity scale				
Ostacher et al., 2021[4] High risk of bias	N = 55 Mean, 4.8 (0.6)	N = 48 Mean, 3.2 (1.3)	N = 42 Mean, 3.0 (1.6)	N = 38 Mean, 3.0 (1.8)
% Participants with ≥ 6-point decrease in CAPS-5 score (responders)				
Ostacher et al., 2021[4] High risk of bias	N = 55 NA	N = 48 NR	N = 42 88%	N = 38 NR
% Participants with response plus no longer meeting *DSM-5* criteria for PTSD (remission)				
Ostacher et al., 2021[4] High risk of bias	N = 55 NA	N = 48 NR	N = 42 48%	N = 38 50%

Abbreviations. DSM-5: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; *NA: not applicable; NR: not reported; PTSD: posttraumatic stress disorder; SD: standard deviation.*

Appendix H. Excluded Studies With Primary Reason for Exclusion

Table H. Excluded Studies With Primary Reason for Exclusion

Reference Information	Primary Reason for Exclusion
Complementary and alternative medicine for posttraumatic stress disorder symptoms: a systematic review. *Journal of Evidence-Based Complementary and Alternative Medicine*. 2014. 19:161-175.	Intervention
Andrews G, Bell C, Boyce P, et al. Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for the treatment of panic disorder, social anxiety disorder and generalised anxiety disorder. *Aust N Z J Psychiatry*. 2018;52(12):1109-1172.	Intervention
Bandelow B, Allgulander C, Baldwin DS, et al. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for treatment of anxiety, obsessive-compulsive and posttraumatic stress disorders - version 3. part I: anxiety disorders. *World J Biol Psychiatry*. 2023;24(2):79-117. doi: 10.1080/15622975.2022.2086295.	Intervention
Bandelow B, Allgulander C, Baldwin DS, et al. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for treatment of anxiety, obsessive-compulsive and posttraumatic stress disorders - version 3. part II: OCD and PTSD. *World J Biol Psychiatry*. 2023;24(2):118-134. doi: 10.1080/15622975.2022.2086296.	Intervention
Banerjee S, Argáez C. Neurofeedback and biofeedback for mood and anxiety disorders: a review of clinical effectiveness and guidelines. Canada's Drug and Health Technology Agency; 2017; https://www.ncbi.nlm.nih.gov/books/NBK531603/. Accessed March 9, 2024.	Intervention
Banushi B, Brendle M, Ragnhildstveit A, et al. Breathwork interventions for adults with clinically diagnosed anxiety disorders: a scoping review. *Brain Sciences*. 2023;13(2). doi: 10.3390/brainsci13020256.	Intervention
Birch, M. Breathing retraining in anxiety and panic disorder. *Australian Nursing & Midwifery Journal*. 2015. 23:31-3.	Publication type
Bisson JI, Berliner L, Cloitre M, et al. The International Society for Traumatic Stress Studies new guidelines for the prevention and treatment of posttraumatic stress disorder: methodology and development process. *J Trauma Stress*. 2019;32(4):475-483. doi: 10.1002/jts.22421.	Publication type
Bisson JI, van Gelderen M, Roberts NP, Lewis C. Non-pharmacological and non-psychological approaches to the treatment of PTSD: results of a systematic review and meta-analyses. *Eur J Psychotraumatol*. 2020;11(1):1795361. doi: 10.1080/20008198.2020.1795361.	Intervention
Bryant RA, Creamer M, O'Donnell M, McFarlane AC, Silove D. A prospective study of rapid breathing and the development of posttraumatic panic disorder. *Psychological Trauma: Theory, Research, Practice, and Policy*. 2014;6(4):370-374. doi: 10.1037/a0034792.	Aim
Chiari G, Reda MA. Cognitive restructuring through biofeedback in agoraphobia. *Italian Journal of Psychology*. 1981;8(3):275-282.	Full-text unavailable
Chisholm D, Sweeny K, Sheehan P, et al. Scaling-up treatment of depression and anxiety: a global return on investment analysis. *Lancet Psychiatry*. 2016;3(5):415-424. doi: 10.1016/S2215-0366(16)30024-4.	Aim

Reference Information	Primary Reason for Exclusion
Courtois CA, Sonis JH, Brown LS, et al. Clinical practice guideline for the treatment of posttraumatic stress disorder (PTSD) in adults. American Psychological Association; 2017; https://www.apa.org/ptsd-guideline. Accessed February 24, 2024.	Publication type
Cuyler RN, Katdare R, Thomas S, Telch MJ. Real-world outcomes of an innovative digital therapeutic for treatment of panic disorder and PTSD: A 1,500 patient effectiveness study. *Front.* 2022;4:976001. doi: https://dx.doi.org/10.3389/fdgth.2022.976001.	Follow-up length
Davies CD, Craske MG. Low baseline pCO2 predicts poorer outcome from behavioral treatment: evidence from a mixed anxiety disorders sample. *Psychiatry Res.* 2014;219(2):311-315. doi: 10.1016/j.psychres.2014.06.003.	Aim
Denney M, Baugh J, Gregory W, Jessop N. Biofeedback therapy for PTSD patients. *VA Practitioner.* 1993;10:65-67.	Full-text unavailable
Domhardt M, Nowak H, Engler S, et al. Therapeutic processes in digital interventions for anxiety: A systematic review and meta-analytic structural equation modeling of randomized controlled trials. *Clin Psychol Rev.* 2021;90:102084. doi: 10.1016/j.cpr.2021.102084.	Intervention
Driessen S, Ponds R, van Alphen SPJ, Nederstigt A, Deckers K, Sobczak S. Treating symptoms of posttraumatic stress in people with dementia: expert consensus using the Delphi method. *Clin Gerontol.* 2023:1-15. doi: 10.1080/07317115.2023.2170842.	Intervention
Fincham GW, Strauss C, Montero-Marin J, Cavanagh K. Effect of breathwork on stress and mental health: A meta-analysis of randomised-controlled trials. *Sci Rep.* 2023;13(1). doi: 10.1038/s41598-022-27247-y.	Intervention
Fonkoue IT, Marvar PJ, Norrholm SD, et al. Acute effects of device-guided slow breathing on sympathetic nerve activity and baroreflex sensitivity in posttraumatic stress disorder. *Am J Physiol Heart Circ Physiol.* 2018;315(1):H141-H149. doi: 10.1152/ajpheart.00098.2018.	Intervention
Freeman M, Nugent SM, Ayers CK, et al. Gulf War illness - a systematic review of therapeutic interventions and management strategies. Evidence Synthesis Program, Health Services Research and Development Service, Office of Research and Development, Department of Veterans Affairs; 2020; https://www.hsrd.research.va.gov/publications/esp/gulf-war-illness.cfm. Accessed February 24, 2024.	Intervention
Gray B, Asrat B, Brohan E, Chowdhury N, Dua T, van Ommeren M. Management of generalized anxiety disorder and panic disorder in general health care settings: new WHO recommendations. *World Psychiatry.* 2024;23(1):160-161. doi: https://dx.doi.org/10.1002/wps.21172.	Publication type
Herhaus B, Conrad R, Petrowski K. Effect of a slow-paced breathing with heart rate variability biofeedback intervention on pro-inflammatory cytokines in individuals with panic disorder - a randomized controlled trial. *J Affect Disord.* 2023;326:132-138. doi: 10.1016/j.jad.2023.01.091.	Intervention
Hoge CW, Chard KM, Yehuda R. US Veterans Affairs and Department of Defense 2023 Clinical Guideline for PTSD-Devolving Not Evolving. *JAMA Psychiatry.* 2024;10:10. doi: https://dx.doi.org/10.1001/jamapsychiatry.2023.4920.	Publication type
ISTSS Guidelines Committee. ISTSS guidelines position paper on complex PTSD in adults. International Society for Traumatic Stress Studies; 2018; https://istss.org/getattachment/Treating-Trauma/New-ISTSS-Prevention-and-	Aim

Reference Information	Primary Reason for Exclusion
Treatment-Guidelines/ISTSS_CPTSD-Position-Paper-(Adults)_FNL.pdf.aspx. Accessed February 25, 2024.	
ISTSS Guidelines Committee. Posttraumatic stress disorder prevention and treatment guidelines: methodology and recommendations. International Society for Traumatic Stress Studies; 2018; https://istss.org/getattachment/Treating-Trauma/New-ISTSS-Prevention-and-Treatment-Guidelines/ISTSS_PreventionTreatmentGuidelines_FNL-March-19-2019.pdf.aspx. Accessed February 25, 2024.	Intervention
Jamison AL, Slightam C, Bertram F, Kim S, Roth WT. Randomized clinical trial of capnometry-assisted respiratory training in veterans with posttraumatic stress disorder hyperarousal. *Psychological Trauma: Theory, Research, Practice and Policy*. 2022;14(5):883-893. doi: https://dx.doi.org/10.1037/tra0000525.	Intervention
Katzman MA, Bleau P, Blier P, et al. Canadian clinical practice guidelines for the management of anxiety, posttraumatic stress and obsessive-compulsive disorders. *BMC Psychiatry*. 2014;14(SUPPL.1). doi: 10.1186/1471-244X-14-S1-S1.	Publication date
Kim S, Roth WT, Wollburg E. Effects of therapeutic relationship, expectancy, and credibility in breathing therapies for anxiety. *Bull Menninger Clin*. 2015;79(2):116-130. doi: 10.1521/bumc.2015.79.2.116.	Intervention
Kowalski J, Elzanowski A, Sliwerski A. A review of selected psychotherapies for PTSD, their efficacy and treatment guidelines in adults. *Psychiatr Pol*. 2023:1-11. doi: https://dx.doi.org/10.12740/PP/OnlineFirst/157105.	Publication type
Koweszko T, de Barbaro B, Izydorczyk B, et al. The position statement of the Working Group on the treatment of post-traumatic stress disorders in adults. *Psychiatr Pol*. 2023;57(4):705-727. doi: 10.12740/PP/166172.	Intervention
Lang AJ, Hamblen JL, Holtzheimer P, et al. A clinician's guide to the 2023 VA/DoD Clinical Practice Guideline for Management of Posttraumatic Stress Disorder and Acute Stress Disorder. *J Trauma Stress*. 2024;37(1):19-34. doi: 10.1002/jts.23013.	Publication type
Lee U, Jung G, Ma E-Y, et al. Toward data-driven digital therapeutics analytics: literature review and research directions. *IEEE/CAA Journal of Automatica Sinica*. 2023;10(1):42-66. doi: 10.1109/jas.2023.123015.	Aim
Lewis C, Roberts NP, Andrew M, Starling E, Bisson JI. Psychological therapies for post-traumatic stress disorder in adults: systematic review and meta-analysis. *Eur J Psychotraumatol*. 2020;11(1):1729633. doi: https://dx.doi.org/10.1080/20008198.2020.1729633.	Intervention
Leyro TM, Versella MV, Yang MJ, Brinkman HR, Hoyt DL, Lehrer P. Respiratory therapy for the treatment of anxiety: Meta-analytic review and regression. *Clin Psychol Rev*. 2021;84:101980. doi: 10.1016/j.cpr.2021.101980.	Intervention
Madhusudhan DK, Glied KN, Nguyen E, Rose J, Bravata DM. Real-world evaluation of a novel technology-enabled capnometry-assisted breathing therapy for panic disorder. *Journal of Mental Health & Clinical Psychology*. 2020;4(4):39-46.	Follow-up length
Martin A, Naunton M, Kosari S, Peterson G, Thomas J, Christenson JK. Treatment guidelines for PTSD: a systematic review. *J*. 2021;10(18):15. doi: https://dx.doi.org/10.3390/jcm10184175.	Study design
Metcalf O, Stone C, Hinton M, et al. Treatment augmentation for posttraumatic stress disorder: A systematic review. *Clinical Psychology: Science and Practice*. 2020;27(1):e12310.	Intervention

Reference Information	Primary Reason for Exclusion
Meuret AE, Hofmann SG, Rosenfield D. Catastrophic appraisal and perceived control as moderators of treatment response in panic disorder. *Int J Cogn Ther.* 2010;3:262-277.	Intervention
Meuret AE, Ritz T. Hyperventilation in panic disorder and asthma: empirical evidence and clinical strategies. *Int J Psychophysiol.* 2010;78(1):68-79. doi: https://dx.doi.org/10.1016/j.ijpsycho.2010.05.006.	Intervention
Meuret AE, Ritz T, Wilhelm FH, Roth WT, Rosenfield D. Hypoventilation therapy alleviates panic by repeated induction of dyspnea. *Biol Psychiatry Cogn Neurosci Neuroimaging.* 2018;3(6):539-545. doi: https://dx.doi.org/10.1016/j.bpsc.2018.01.010.	Intervention
Meuret AE, Rosenfield D, Hofmann SG, Suvak MK, Roth WT. Changes in respiration mediate changes in fear of bodily sensations in panic disorder. *J Psychiatr Res.* 2009;43(6):634-641. doi: 10.1016/j.jpsychires.2008.08.003.	Intervention
Meuret AE, Wilhelm FH, Roth WT. Respiratory biofeedback-assisted therapy in panic disorder. *Behav Modif.* 2001;25(4):584-605. doi: 10.1177/0145445501254006.	Intervention
Meuret AE, Wilhelm FH, Ritz T, Roth WT. Feedback of end-tidal pCO2 as a therapeutic approach for panic disorder. *J Psychiatr Res.* 2008;42(7):560-568.	Intervention
Meuret AE, Wilhelm FH, Roth WT. Respiratory biofeedback-assisted therapy in panic disorder. *Behav Modif.* 2001;25(4):584-605. doi: 10.1177/0145445501254006.	Intervention
Michael T, Schanz CG, Mattheus HK, et al. Do adjuvant interventions improve treatment outcome in adult patients with posttraumatic stress disorder receiving trauma-focused psychotherapy? A systematic review. *Eur J Psychotraumatol.* 2019;10(1):1634938. doi: https://dx.doi.org/10.1080/20008198.2019.1634938.	Intervention
Miles LW, Valentine JL, Mabey LJ, et al. A systematic review of evidence-based treatments for adolescent and adult sexual assault victims. *J Am Psychiatr Nurses Assoc.* 2023:10783903231216138. doi: 10.1177/10783903231216138.	Intervention
Moore BA, Pujol L, Waltman S, Shearer DS. Management of post-traumatic stress disorder in veterans and military service members: a review of pharmacologic and psychotherapeutic interventions since 2016. *Current Psychiatry Reports.* 2021;23(2):9. doi: https://dx.doi.org/10.1007/s11920-020-01220-w.	Publication type
National Institute for Health and Care Excellence. Post-traumatic stress disorder. 2018; https://www.nice.org.uk/guidance/ng116. Accessed February 24, 2024.	Intervention
National Institute for Health and Care Excellence. Generalised anxiety disorder and panic disorder in adults: management. 2020; https://www.nice.org.uk/guidance/cg113. Accessed February 24, 2024.	Intervention
Nelson KL, Lu SE, Oken T, Lehrer PM, Feldman JM. Further exploration of treatment response in Latinos with comorbid asthma and panic disorder: a brief report of HRV and ETCO2 as potential mediators of treatment response. *Appl Psychophysiol Biofeedback.* 2020;45(2):67-74. doi: https://dx.doi.org/10.1007/s10484-020-09454-3.	Intervention
Newman MG, Szkodny LE, Llera SJ, Przeworski A. A review of technology-assisted self-help and minimal contact therapies for anxiety and depression: is human contact necessary for therapeutic efficacy? *Clin Psychol Rev.* 2011;31(1):89-103. doi: 10.1016/j.cpr.2010.09.008.	Publication type
O'Neil ME, Cheney TP, Yu Y, et al. Systematic review: pharmacologic and nonpharmacologic base for the PTSD Trials Standardized Data Repository.	Publication type

Reference Information	Primary Reason for Exclusion
Agency for Healthcare Research and Quality; 2023; https://effectivehealthcare.ahrq.gov/products/ptsd-pharm-non-pharm-treatment/research. Accessed February 24, 2024.	
Olff M, Amstadter A, Armour C, et al. A decennial review of psychotraumatology: what did we learn and where are we going? *Eur J Psychotraumatol*. 2019;10(1):1672948. doi: 10.1080/20008198.2019.1672948.	Publication type
Ostacher MJ, Cifu AS. Management of posttraumatic stress disorder. *JAMA*. 2019;321(2):200-201. doi: https://dx.doi.org/10.1001/jama.2018.19290.	Intervention
Papola D, Ostuzzi G, Tedeschi F, et al. Comparative efficacy and acceptability of psychotherapies for panic disorder with or without agoraphobia: Systematic review and network meta-Analysis of randomised controlled trials. *Br J Psychiatry*. 2022;221(3):507-519. doi: 10.1192/bjp.2021.148.	Intervention
Perna G. Panic disorder: from psychopathology to treatment. *Journal of Psychopathology*. 2012;18(1):82-91.	Publication type
Perna G, Caldirola D. Management of treatment-resistant panic disorder. *Current Treatment Options in Psychiatry*. 2017;4(4):371-386. doi: 10.1007/s40501-017-0128-7.	Intervention
Phelps AJ, Lethbridge R, Brennan S, et al. Australian guidelines for the prevention and treatment of posttraumatic stress disorder: Updates in the third edition. *Aust N Z J Psychiatry*. 2022;56(3):230-247. doi: 10.1177/00048674211041917.	Intervention
Phoenix Australia. Australian guidelines for the prevention and treatment of acute stress disorder, posttraumatic stress disorder and complex posttraumatic stress disorder. 2021; https://www.phoenixaustralia.org/australian-guidelines-for-ptsd/. Accessed February 25, 2024.	Intervention
Pierce ZP, Black JM. The neurophysiology behind trauma-focused therapy modalities used to treat post-traumatic stress disorder across the life course: A systematic review. *Trauma Violence Abuse*. 2023;24(2):1106-1123. doi: 10.1177/15248380211048446.	Intervention
Ramakers I, Van Den Houte M, Van Oudenhove L, Van den Bergh O, Bogaerts K. End-tidal CO2 in patients with panic disorder, stress-related or functional syndromes, versus healthy controls. *Appl Psychophysiol Biofeedback*. 2023;48(2):149-157. doi: https://dx.doi.org/10.1007/s10484-022-09573-z.	Aim
Roberts NP, Lotzin A, Schafer I. Psychological treatment of PTSD with comorbid substance use disorder (SUD): expert recommendations of the European Society for Traumatic Stress Studies (ESTSS). *Eur J Psychotraumatol*. 2023;14(2):2265773. doi: https://dx.doi.org/10.1080/20008066.2023.2265773.	Intervention
Rosaura Polak A, Witteveen AB, Denys D, Olff M. Breathing biofeedback as an adjunct to exposure in cognitive behavioral therapy hastens the reduction of PTSD symptoms: a pilot study. *Appl Psychophysiol Biofeedback*. 2015;40(1):25-31. doi: https://dx.doi.org/10.1007/s10484-015-9268-y.	Intervention
Roth WT. Physiological markers for anxiety: panic disorder and phobias. *Int J Psychophysiol*. 2005;58(2-3):190-198. doi: 10.1016/j.ijpsycho.2005.01.015.	Intervention
Roth WT. Diversity of effective treatments of panic attacks: what do they have in common? *Depress Anxiety*. 2010;27(1):5-11. doi: 10.1002/da.20601.	Publication type
Saguil A. Psychological and pharmacologic treatments for adults with PTSD. *Am Fam Physician*. 2019;99(9):577-583.	Intervention
Saiz PA, Florez G, Arrojo M, et al. Clinical practice guideline on pharmacological and psychological management of adult patients with an anxiety disorder and	Intervention

Reference Information	Primary Reason for Exclusion
comorbid substance use. *Adicciones*. 2022;34(2):157-167. doi: 10.20882/adicciones.1548.	
Schmidt NB, Keough ME. Treatment of panic. *Annual Review of Clinical Psychology*. Vol 62010:241-256.	Intervention
Schoenberg PLA, David AS. Biofeedback for psychiatric disorders: A systematic review. *Applied Psychophysiology Biofeedback*. 2014;39(2):109-135. doi: 10.1007/s10484-014-9246-9.	Intervention
Schuman DL, Killian MO. Pilot study of a single session heart rate variability biofeedback intervention on veterans' posttraumatic stress symptoms. *Appl Psychophysiol Biofeedback*. 2019;44(1):9-20. doi: 10.1007/s10484-018-9415-3.	Intervention
Spottswood M, Fortney J, Chen JA, Davydow D, Huang H. Posttraumatic stress disorder in the primary care setting: summary of recommended care. *Harv Rev Psychiatry*. 2019;27(2):87-93. doi: 10.1097/HRP.0000000000000201.	Publication type
Stetz MC, Folen RA, Yamanuha BK. Technology complementing military behavioral health efforts at tripler army medical center. *J Clin Psychol Med Settings*. 2011;18(2):188-195. doi: 10.1007/s10880-011-9246-3.	Publication type
ter Harmsel JF, Noordzij ML, Goudriaan AE, et al. Biocueing and ambulatory biofeedback to enhance emotion regulation: A review of studies investigating non-psychiatric and psychiatric populations. *Int J Psychophysiol*. 2021;159:94-106. doi: 10.1016/j.ijpsycho.2020.11.009.	Intervention
Tolin DF, Davies CD, Moskow DM, Hofmann SG. Biofeedback and neurofeedback for anxiety disorders: A quantitative and qualitative systematic review. *Advances in Experimental Medicine and Biology*. Vol 11912020:265-289.	Intervention
Tunnell NC, Ritz T, Wilhelm FH, Roth WT, Meuret AE. Habituation or normalization? experiential and respiratory recovery from voluntary hyperventilation in treated versus untreated patients with panic disorder. *Behav Ther*. 2021;52(1):124-135. doi: 10.1016/j.beth.2020.03.003.	Intervention
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Appendix I. Description of Payer Policies

Table I1. Overview of Coverage Criteria for Digital Health Technologies and Freespira

Policy Author Last Review Date	Policy Terminology and Definition of Digital Health Technologies	Medical Necessity Criteria for Digital Health Technologies	Freespira Coverage
Private payers			
Aetna[15] July 17, 2024	Prescription digital therapeutics	Only covers FDA-approved or FDA-cleared mobile apps for contraception based on fertility awareness, when prescribed by a treating provider, per federal preventive care mandates	Not covered • Considered experimental and investigational • Insufficient evidence in published peer-reviewed literature on effectiveness
Anthem Blue Cross and Blue Shield (formerly Empire BlueCross BlueShield)[14] August 8, 2024	Mobile device-based health management applications Practitioner-prescribed software applications for health management purposes when used on a mobile device with the intent to evaluate, diagnose, or treat an illness, injury, disease, or its symptoms.	When the following criteria have been met: • Criteria to evaluate the MSA: o Approved or cleared by FDA o Credible scientific evidence that permits reasonable conclusions regarding the impact of the MSA on health outcomes o MSA proven materially to improve the net health outcome or be as beneficial as established alternative • Criteria to evaluate the appropriateness of the MSA for the individual: o MSA prescribed by a health care practitioner o Documentation supporting that MSA ordered for a covered purpose, and in accordance with accepted standard of medical practice o Requested MSA is not primarily for the convenience of the individual, prescribing clinician, caregiver, or other health care provider	Not covered Available evidence: • Lacks comparisons to standards of care • Small sample sizes • Subject to bias due to loss to follow-up

Policy Author Last Review Date	Policy Terminology and Definition of Digital Health Technologies	Medical Necessity Criteria for Digital Health Technologies	Freespira Coverage
Highmark Inc. No month provided 2024[17] June 2024[119]	Prescription digital therapeutics • Technology-based therapeutic interventions for the treatment of medical and behavioral conditions • Used as a part or whole of a treatment plan for appropriate health diagnoses that fall within the scope of approved use of the digital health software	FDA-approved digital therapeutics prescribed by a licensed health care professional for therapeutic intervention may be considered medically necessary when the following criteria are met: • Used within approved indications • Prescribed by a provider for whom the condition is within the scope of their practice • Individual must be at least 18 years of age, unless the digital therapeutic is designed and approved for pediatric use • Only used for outpatient care • Individual must be able to reasonably interact with the software • Approved by Highmark New Technology Advisory Committee	Covered • Commercial and Affordable Care Act members aged 18 years and older in Delaware, Pennsylvania, and West Virginia • Used to treat mild to moderate panic disorder and mild symptoms of PTSD • Not intended as a standalone intervention but as an adjunct to treatment with a mental health professional
Molina Healthcare[16] April 10, 2024	Prescription digital therapeutics • FDA-approved or FDA-cleared clinician-prescribed software applications when used on a mobile device for health management purposes with the intent to evaluate, diagnose, or treat an illness, injury, disease, or its symptoms	Prescription digital therapeutics considered experimental, investigational, and unproven due to insufficient clinical evidence and peer-reviewed medical literature establishing long-term safety, efficacy, and effect on health outcomes	Not covered • Experimental, investigational, and unproven • Need studies with larger sample sizes that compare Freespira with standard treatment options

Policy Author Last Review Date	Policy Terminology and Definition of Digital Health Technologies	Medical Necessity Criteria for Digital Health Technologies	Freespira Coverage
State Medicaid programs			
Oregon (Oregon Health Plan) June 28, 2023[19] August 17, 2023[20]	Not provided	Not provided	Not covered • Device in early stages of evaluation and evidence does not yet support its use • Literature on effect of Freespira consists mostly of small cohort studies • Available studies subject to bias from loss of follow-up • Lack of RCTs comparing device to standard treatments

Abbreviations. FDA: US Food and Drug Administration; MSA: mobile software application; PTSD: posttraumatic stress disorder; RCT: randomized controlled trial.

Table I2. Overview of Coverage Criteria for Biofeedback

Policy Author Last Review Date	Medical Necessity Criteria for Biofeedback	Biofeedback Coverage[a]	Not Covered (Considered Experimental or Investigational)
Private payers			
Aetna[15] October 11, 2024	Considered medically necessary for the following conditions: • Cancer pain • Chronic constipation secondary to dyssynergic defecation • Fecal incontinence • Irritable bowel syndrome • Levator ani syndrome (also known as anorectal pain syndrome) • Migraine and tension headaches • Neuromuscular rehabilitation of stroke and traumatic brain injury • Refractory severe tinnitus • Temporomandibular joint syndrome • Urinary incontinence	CPT codes 90834, 90875, 90876, 90901, 90912, and 90913 covered if selection criteria are met	• For many conditions, including panic disorder and PTSD, because effectiveness has not been established • Home biofeedback for any indication
Anthem Blue Cross and Blue Shield (formerly Empire BlueCross BlueShield)[30] May 9, 2024	Considered medically necessary when the following criteria have been met: • Supervised by a physician or licensed practitioner **and** • Used as a treatment for at least one of the following conditions: o Cancer pain o Chronic back pain o Chronic constipation o Fecal incontinence o Levator ani syndrome o Migraine or tension headaches o Urinary incontinence	CPT codes 90875, 90876, 90901, 90912, and 90913 used when services are medically necessary for biofeedback techniques	• When criteria for medical necessity are not met and for all other indications, including PTSD • Neurofeedback, also known as EEG biofeedback, for all indications • Use of home biofeedback devices

Policy Author Last Review Date	Medical Necessity Criteria for Biofeedback	Biofeedback Coverage[a]	Not Covered (Considered Experimental or Investigational)
Cigna Healthcare[31] November 15, 2023	• Biofeedback performed by a licensed health care professional considered medically necessary for any of the following conditions: o Chronic constipation with dyssynergic defecation (adults only) o Fecal incontinence for patients o Urinary incontinence (children and adults) o Migraine and tension headaches (children and adults) o Muscle re-education of specific extremity muscle groups for treating pathological muscle abnormalities o Refractory levator ani syndrome with dyssynergic defecation • Patients must be cognitively intact and willing and motivated to learn and practice the tasks needed to correct or improve their problems • Written treatment plan with: o Specific diagnosis or conditions to be treated o Long- and short-term goals o Measurable objectives o Time frame and frequency of treatment in which goals and objectives will be achieved	• CPT codes 90901, 90912, 90913 considered medically necessary when criteria in policy statement are met • HCPCS code E1399 used to report the Leva Pelvic Health System device	• Biofeedback for any indication other than those covered under medical necessity criteria • Neurofeedback or EEG biofeedback for any indication • In-home biofeedback devices, except the Leva Pelvic Health System for women with urinary incontinence
Excellus BlueCross BlueShield[32] June 20, 2024	Considered medically appropriate for the following conditions after conventional treatment has unsuccessful: • Migraine and tension headaches • Dyssynergic constipation	• CPT codes 90875, 90876, 90901, 90912, and 90913 used when criteria for medical necessity are met • HCPCS code E0746 used when criteria for medical necessity are met • Recommended treatment course for patients with migraine and tension-type	Biofeedback for all other indications

Policy Author Last Review Date	Medical Necessity Criteria for Biofeedback	Biofeedback Coverage[a]	Not Covered (Considered Experimental or Investigational)
		headaches: up to 20 office-based biofeedback sessions • Recommended treatment course for patients with dyssynergic constipation: up to 6 biofeedback sessions over 3 months • Sessions beyond the allowed number require documentation of therapeutic effectiveness before further sessions considered for coverage	
Highmark Inc.[33] April 2024	• Biofeedback may be considered medically necessary for: o Dyssynergic constipation o Migraine and tension headaches o Urinary incontinence • Biofeedback using capnometry-guided respiratory intervention (e.g., Freespira) may be considered medically necessary as part of the overall treatment plan for: o Adults (age 18 years and older) diagnosed with panic disorder or PTSD **and** o Physically and cognitively capable of participating in the treatment	• CPT codes 90875, 90876, 90901, 90912, and 90913 used when criteria for medical necessity are met • HCPCS code A9279 or E0746 used when criteria for medical necessity are met • Freespira available to commercial and Affordable Care Act members in Delaware, Pennsylvania, and West Virginia	Biofeedback not meeting medical necessity criteria
Medicare			
Centers for Medicare & Medicaid Services[26,27] No effective date July 1, 2011	Biofeedback covered when reasonable and necessary and conventional treatments have failed for: • Retraining of specific muscle groups • Pathological muscle abnormalities of spasticity • Incapacitating muscle spasm or weakness • Stress or urge urinary incontinence	Not provided	Biofeedback therapy for: • Ordinary muscle tension • Psychosomatic conditions • Home use

Policy Author Last Review Date	Medical Necessity Criteria for Biofeedback	Biofeedback Coverage[a]	Not Covered (Considered Experimental or Investigational)
State Medicaid programs			
California (Medi-Cal)[25] October 2024	Not covered	CPT codes 90875, 90876, 90901, 90912, and 90913 classified as non-benefit	Not provided
Massachusetts (MassHealth)[34] August 1, 2024	Not covered	Does not pay for services billed under CPT codes 90875, 90876, 90901, 90912 or 90913	Not provided
New Jersey (NJ FamilyCare) December 5, 2022[24,28] August 1, 2024[120]	• Not covered for beneficiaries eligible for NJ FamilyCare-Plan D, NJ FamilyCare-Plan D for adults, or NJ FamilyCare-Plan I[b] • Not mentioned as service available or unavailable for beneficiaries eligible for other Medicaid plans	CPT code 90901 on list of Medicaid fee for services codes for outpatient hospital billing	Not provided
New York[35] January 1, 2024	Not covered	CPT codes 90875, 90876, and 90901 on list of never pay procedures under ambulatory patient group reimbursement, no alternative payment available, added to list on July 1, 2010	Not provided
Oregon (Oregon Health Plan) October 21, 2020[36] November 17, 2022[37] October 1, 2024[114]	Biofeedback covered for: • Migraine and tension headaches • Palliative care service for treatment of cancer pain	CPT codes 90875, 90876, and 90901 for covered conditions	• No evidence supporting use of biofeedback or neurofeedback for the treatment of mental health conditions, including PTSD and childhood trauma • Insufficient evidence of effectiveness for CPT codes 90912 and 90913
Texas[38,39] October 2024	• Covered for individuals 4 years of age and older with the following conditions: o Fecal incontinence o Migraine and tension headaches o Urinary incontinence	• Prior authorization required, with documentation of the following: o Conventional treatments that were given but not successful o Statement from prescribing physician that client is capable of understanding requirements and agrees to actively participate in biofeedback sessions	• Psychological, psychophysiological, and behavioral health therapy • Psychosomatic conditions • Neurofeedback, such as but not limited to EEG

Policy Author Last Review Date	Medical Necessity Criteria for Biofeedback	Biofeedback Coverage[a]	Not Covered (Considered Experimental or Investigational)
		○ Name and certification information of person performing the training (staff member who is certified by Biofeedback Certification International Alliance must perform services) ○ Documentation to support the specific type of biofeedback requested • Services for fecal or urinary incontinence reimbursed using CPT codes 90901, 90912, and 90913 • Services for migraine or tension headache reimbursed using CPT code 90901 • Initial request may include up to 12 visits and not exceed a total duration of 12 weeks • After client completes initial biofeedback treatment course, prior authorization may be considered for 6 follow-up sessions, not to exceed 3 sessions per week and a total duration of 8 weeks; must include documentation of each original symptom and how it has improved • Limited to 1 service per day • Services limited to maximum of 18 sessions rendered by any provider for the lifetime of each client for each condition • Any device used during a biofeedback session considered part of the procedure, not reimbursed separately	• Biofeedback performed in the home setting • Treatment for muscle tension, except tension headache • Experimental or investigational biofeedback services or procedures

Policy Author Last Review Date	Medical Necessity Criteria for Biofeedback	Biofeedback Coverage[a]	Not Covered (Considered Experimental or Investigational)
Washington state (Apple Health) October 1, 2024[40] October 9, 2024[41]	Not provided	• CPT code 90912 covered, maximum allowable non-facility and facility fees $47.37 and $24.06, respectively • CPT code 90913 covered, maximum allowable non-facility and facility fees $18.46 and $13.43, respectively • CPT codes 90875, 90876, and 90901 not covered	Not provided

Notes. [a] See Appendix J for description of CPT and HCPCS codes. [b] NJ FamilyCare-Part D is the state-operated program that provides managed care coverage to uninsured children through the age of 18 with gross family incomes above 200% and not in excess of 350% of the federal poverty level; NJ FamilyCare-Part D for adults is the state-operated program that provides a benefit package through managed care organizations, supplemented by services provides on a fee-for-service basis, to specified parents or caretakers of children enrolled in NJ FamilyCare; NJ FamilyCare-Part I is the state-operated program that provides a Plan D benefit package on a fee-for-service basis to specified parents or caretakers of children enrolled in NJ FamilyCare.

Abbreviations. CPT: Current Procedural Terminology; EEG: electroencephalography; HCPCS: Healthcare Common Procedure Coding System; PTSD: posttraumatic stress disorder.

Appendix J. Relevant Codes

Table J1. Relevant Codes for Freespira

Code	Description
ICD-10-CM codes	
F40.01	Agoraphobia with panic disorder
F41.0	Panic disorder [episodic paroxysmal anxiety]
F43.1	Posttraumatic stress disorder
F43.10	Posttraumatic stress disorder, unspecified
F43.11	Posttraumatic stress disorder, acute
F43.12	Posttraumatic stress disorder, chronic
CPT codes	
90875	Individual psychophysiological therapy incorporating biofeedback training by any modality (face-to-face with the patient), with psychotherapy (e.g., insight oriented, behavior modifying, or supportive psychotherapy), 30 minutes
90876	Individual psychophysiological therapy incorporating biofeedback training by any modality (face-to-face with the patient), with psychotherapy (e.g., insight oriented, behavior modifying, or supportive psychotherapy), 45 minutes
90901	Biofeedback training by any modality
91999	Unlisted special service, procedure or report [when specified as a mobile-based health management software application]
HCPCS codes	
A9279	Monitoring/feature device, stand-alone or integrated, any type, includes all accessories, components, and electronics, not otherwise classified
A9291	Prescription digital cognitive and/or behavioral therapy, FDA-cleared, per course of treatment
A9999	Miscellaneous durable medical equipment supply or accessory, not specified
E1399	Durable medical equipment, miscellaneous [when specified as a mobile-based health management software application]

Abbreviations: CPT: Current Procedural Terminology; HCPCS: Healthcare Common Procedure Coding System; ICD-10-CM: International Classification of Diseases, Tenth Revision, Clinical Modification.

Table J2. Relevant Codes for Biofeedback for Other Conditions

Code	Description
CPT codes	
90912	Biofeedback training, perineal muscles, anorectal or urethral sphincter, including electromyography and/or manometry, when performed; initial 15 minutes of one-on-one physician or other qualified health professional contact with the patient
90913	Biofeedback training, perineal muscles, anorectal or urethral sphincter, including electromyography and/or manometry, when performed; each additional 15 minutes of one-on-one physician or other qualified health professional contact with the patient
HCPCS codes	
E0746	Electromyography, biofeedback device

Abbreviations: CPT: Current Procedural Terminology; HCPCS: Healthcare Common Procedure Coding System;