



## IT'S NOT "ALL IN YOUR HEAD"

A Physiological Approach to  
Treating Panic Attacks and PTSD

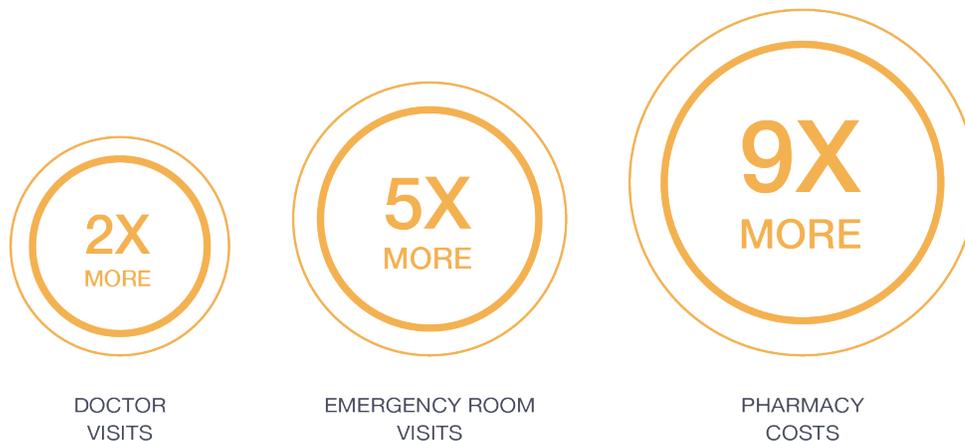
# INTRODUCTION

Panic attacks, panic disorder, and Post-Traumatic Stress Disorder (PTSD) are debilitating conditions that exact a significant toll on patients, their families, their employers, the health care system, and society at large. Existing treatment options, such as psychotherapy and medications, do not bring full or lasting relief to a large proportion of sufferers. Nor do they adequately address the immense cost burden to employers and the healthcare system. As a result, health plans and employers need new approaches to the treatment of panic attacks and PTSD symptoms that are safe and effective, have limited side effects, can be delivered remotely, and most importantly, that address the underlying physiological factors that create risk for developing these two conditions.

## The Need

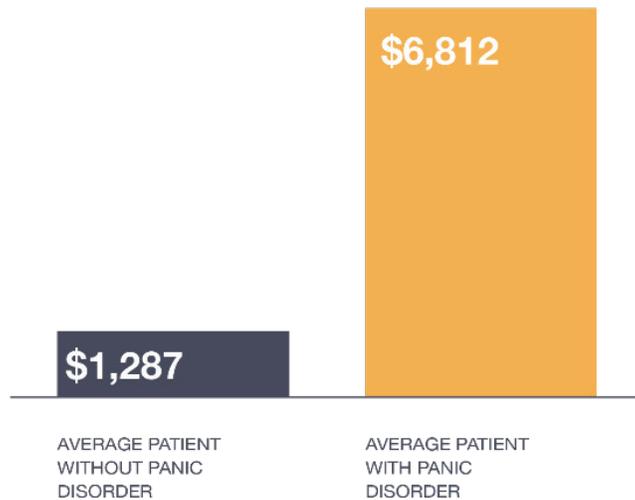
More than 27 million people in the United States had a panic attack last year and 17.1 million of those have frequent panic attacks.<sup>1</sup> Patients with panic attacks suffer tremendous negative impact to their quality of life, as distressing symptoms – including chest pain, heart palpitations, shortness of breath, dizziness, or abdominal distress – and the avoidance of triggering events affect social and work functioning. These patients face great obstacles to reach their full potential and enjoy everyday life. In addition, these patients consume a disproportionate share of cost to the health care system.

### PATIENTS WITH PANIC ATTACKS



Patients who experience repeated, intense panic attacks are usually diagnosed as having panic disorder, a type of anxiety disorder. Patients with panic disorder require two times the doctor visits, five times more emergency room visits and nine times the pharmacy costs of patients who don't suffer from panic attacks, when controlling for overall health status.

<sup>1</sup> Kessler et al, The epidemiology of panic attacks, panic disorder, and agoraphobia in the National Comorbidity Survey Replication. Arch Gen Psychiatry. 2006 Apr;63(4):415-24. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1958997> Cost Data provided by Health Lumen



The overall annual health care cost of an average patient with panic disorder is \$6,812, versus \$1,287 for an average patient in a medically matched control group.<sup>2</sup>

Meanwhile, 8.7 million people in the U.S. struggle with Post-Traumatic Stress Disorder, including 470,000 military veterans. The disruption to their lives is devastating, affecting everything from sleep, to ability to work, to personal relationships. Data from the Veterans<sup>3</sup> Administration indicate that veterans with PTSD cost this system more than four times as much as those with other behavioral health conditions.

The cost to employers of letting the conditions go untreated is significant. In a survey<sup>4</sup> of 2,074 adults that measured workplace absenteeism and presenteeism (the need to cut back on work due to a health condition), panic was in the top five of all health conditions. Workers suffering with panic disorders averaged 5.1 impairment days in a 30-day span. This is compared to 10.9 days for cancer and 6.6 days for heart disease. A World Health Organization analysis<sup>5</sup> of 'Days out of Role' (defined as total inability to work or carry out normal activities because of health condition) ranked panic disorder as the number one most impairing health condition among high income nations, at an average of 45.6 days per year, followed closely by PTSD and bipolar disorder, but greatly exceeding cancer (31.5 days), cardiovascular illness (27.9 days), and migraine/headache (32.3 days).

## Limits of Current Therapies

Existing treatment options include medications and psychotherapy. But a new treatment is needed in the marketplace that can help address remaining unmet needs. While psychotherapy is useful for some patients with panic attacks and PTSD, it is not appropriate or sufficient for all patients. The long duration of treatment can pose obstacles for access, affordability as well as adherence over time, and high dropout rates are reported for talk therapy, particularly the exposure-based therapies most commonly used to address PTSD. Long wait times for appointments and poor provider access in certain regions of the country, particularly in rural areas, can create barriers for many patients. In addition, recovery may fall short of remission, leaving patients with reduced but still life-impairing symptoms.

<sup>2</sup> Cost Data provided by Health Lumen.

<sup>3</sup> <https://www.ncbi.nlm.nih.gov/books/NBK224872/> Treatment for Posttraumatic Stress Disorder in Military and Veteran Populations: Final Assessment.

<sup>4</sup> Kessler RC, Greenberg PE, Mickelson KD, Meneades LM, Wang PS. The effects of chronic medical conditions on work loss and work cutback. *J Occup Environ Med.* 2001; 43:218-225.

<sup>5</sup> Alonso J, Petukhova M, Vilagut G, et al. Days out of role due to common physical and mental health conditions: results from the WHO World Mental Health surveys. *Mol Psychiatr.* 2011; 16(12):1234-1246.

Medication therapy includes several FDA-approved drugs, including several antidepressants approved for panic disorder and PTSD, and benzodiazepines for short-term use with panic. However, long term use of benzodiazepines increases risk of abuse/addiction, and individuals with panic and PTSD have elevated rates of lifetime substance use disorder. Shortcomings of the anti-depressants include side effect burden which can include weight gain, sexual dysfunction, and nausea. These side effects as well as the several weeks often needed to show benefit can compromise adherence. Moreover, half of patients on drug therapy discontinue treatment within six months.<sup>6</sup> And for all classes of medication, relapse rates are high, up to 90% at six years, indicating that extended medication treatment is not effective over the long term.

## Meeting the Moment: COVID-19

The coronavirus pandemic has accelerated the demand for mental health services, especially for panic attacks. Based on a Google Trends analysis, researchers have discovered a major jump in searches related to anxiety, panic attacks, and treatments for panic attacks. With many provider offices closed for extended periods due to the crisis, demand has grown for remote treatment.

While telehealth for all specialties has grown substantially to a high of 14 percent in May 2020, behavioral health has by far grown the fastest. According to a study by the Commonwealth Fund<sup>7</sup>, 41 percent of behavioral health visits were conducted remotely as of October 2020, versus an average of 6 percent across all specialties. The baseline of telehealth visits pre-pandemic was less than 1 percent.

With pressure on providers, there increasingly exists an unfilled niche in the marketplace for remote therapies that allow patients to take control of managing their chronic behavioral health conditions, particularly panic attacks, and PTSD.

## A Symptom-Free Future

Current treatments for panic attacks and PTSD are leaving hundreds of thousands, and perhaps millions, of patients behind. A new approach to treatment can close the gap for patients who have failed other therapies, need to augment their current treatment, or who are currently untreated for their condition. This approach must be supported by both research and real-world data, and must be accessible to patients no matter where they live. Improving the standard of care for patients means improving access, shortening the duration of treatment and improving the durability of the therapy's benefits. At a time when demand for treatments is high, provider resources are stretched, and the country is in the grips of an epidemic of prescription drug misuse and abuse, digital, at-home therapies are crucial additions to the therapeutic toolbox.

One important consideration is the unmet need of patients who are reluctant to seek psychotherapy or drug treatment due to stigma. Patients may fear labels and misconceptions associated with seeing a therapist or may fear dependence on drug therapy. Some patients insist they should be able to overcome their conditions on their own but may find that the price paid is a life narrowed by avoidance. Many have been told their conditions are just "in their head." But emerging science shows that physiological factors play a key role in determining which patients are most at risk for panic attacks and PTSD. This data has helped researchers to zero in on an approach that confronts these physiological symptoms head on, helping patients to develop the self-management skills they need to ward off and prevent panic attacks and acute symptoms of PTSD.

<sup>6</sup> Anna Vlahiotis, MA; Scott T. Devine, PhD et al  
Discontinuation Rates and Health Care Costs in Adult Patients Starting Generic Versus Brand SSRI or SNRI Antidepressants in Commercial Health Plans. *Journal of Managed Care Pharmacy JMCP* March 2011 Vol. 17, No. 2.

<sup>7</sup> <https://www.commonwealthfund.org/blog/2020/using-telehealth-meet-mental-health-needs-during-covid-19-crisis>

## FREESPIRA: A NEW APPROACH

The symptoms of panic attacks can be frightening. Panic attacks are a key component of the diagnosis of panic disorder, but recurrent panic attacks are also present in some 50% to 75% of PTSD patients. Symptoms such as chest tightness, a racing heart, shortness of breath, dizziness, lightheadedness, weakness, unsteadiness, and numbness often send patients to the emergency room. These symptoms are often initially misinterpreted in the ED as a medical emergency, only to be later ruled out as a cardiac or neurological event. This is often the point at which patients are told their symptoms are 'all in your head,' or are referred out to a primary care or medical specialist for testing or follow up. However, multiple studies show that panic patients exhibit respiratory irregularities such as chronic hyperventilation, sighing, and breath-holding compared to the general population, indicating important underlying physiological factors.<sup>8</sup>

### The Role of Carbon Dioxide

In fact, panic disorder and PTSD are both associated with carbon dioxide (CO<sub>2</sub>) hypersensitivity. This hypersensitivity sets the stage for panic attacks, bodily and psychological stress, dissociation, exaggerated startle reflex and posttraumatic flashbacks (in the case of PTSD). Some patients are more sensitive to CO<sub>2</sub> than others. In experimental lab settings, researchers have established that most panic sufferers (and close relatives) react with pronounced fear and physiological distress when exposed to a single breath of air with high CO<sub>2</sub> concentration, compared to normal populations. A double-blind, randomized control study of reactivity to CO<sub>2</sub> challenge showed that diagnosed PTSD patients were highly reactive to 35% CO<sub>2</sub> but not to a placebo gas mixture, while controls were largely unaffected.<sup>9</sup> In addition, soldiers who demonstrated high distress during CO<sub>2</sub> challenge were found to be at higher risk than non-reactors for developing PTSD while serving in conflict zones.<sup>10</sup>

Despite this unique physiological profile behind panic attacks, the most commonly recommended psychiatric treatments have little or no relation to respiratory physiology and CO<sub>2</sub> hypersensitivity. Instead, treatment approaches have focused on altering neurotransmitter balance (drug treatment with benzodiazepines and antidepressants) or on modifying thoughts and feelings (cognitive behavioral therapy). However, building on the underlying science that directly links CO<sub>2</sub> hypersensitivity to panic disorder, a recently developed FDA-cleared digital therapeutic called Freespira precisely targets the symptoms of panic disorder and PTSD that severely limit patients' quality of life.

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A new approach to treatment can close the gap for patients who have failed other therapies, need to augment their current treatment, or who are currently untreated for their condition.

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<sup>8</sup> Abelson J.L., Weg J.G., Nesse R.M., et al. (2001), Persistent respiratory irregularity in patients with panic disorder, *Biol. Psychiatry*, 49(7):588-595. Martinez J.M., Kent J.M., Coplan J.D., et al. (2001), Respiratory variability in panic disorder. *Depress. Anxiety*, 14(4):232-237. Caldirola D., Bellodi L., Caumo A., et al. (2004), Approximate entropy of respiratory patterns in panic disorder, *Am J Psychiatry*, 161(1):79-87.

<sup>9</sup> Kellner M, Muhtz C et al, Effects of 35% carbon dioxide (CO<sub>2</sub>) inhalation in patients with post-traumatic stress disorder: A double-blind, randomized, placebo-controlled cross-over trial, *Journal of Psychiatric Research*, 96 (2018) 260-264.

<sup>10</sup> Telch MJ, Rosenfield D, et al, Emotional Reactivity to a Single Inhalation of 35% Carbon Dioxide and Its Association With Later Symptoms of Posttraumatic Stress Disorder and Anxiety in Soldiers Deployed to Iraq, *ARCH GEN PSYCHIATRY/ VOL 69 (NO. 11), NOV 2012*



## What is Freespira?

Freespira is a breakthrough treatment that normalizes CO<sub>2</sub> and respiratory rates in a single 28-day treatment course, resulting in significant reductions in symptoms, high remission rates and significantly lower total medical costs. The Freespira platform combines a proprietary sensor, a nasal sampling cannula, a connected tablet and proprietary software. The treatment measures respiration rate and exhaled CO<sub>2</sub> levels in real time, graphically displaying these physiological parameters to the patient while guiding them to regulate their exhaled CO<sub>2</sub> level and respiration rate. These twice daily, 17-minute treatment sessions normalize breathing patterns, a transformation that has been shown to eliminate or reduce panic and PTSD symptoms in multiple clinical trials. The Freespira platform includes telehealth training/coaching services throughout the 28-day treatment protocol to guide the patient to maximum benefit.

A first-in-class digital therapeutic, Freespira is cleared by the FDA to specifically treat the symptoms of panic disorder and PTSD. The treatment has not been studied as a treatment for other anxiety disorders or mental health conditions. Freespira develops self-management skills that are learned and then available via 'muscle memory' long after the formal treatment has ended.

During a 17-minute session, the patient inhales and exhales in synch with rising and falling audio tones, while changing their breath volume to move and keep their exhaled CO<sub>2</sub> value in the normal zone, guided by a graphical display on the Freespira tablet. Weekly telehealth coaching provides support, encouragement and guidance for the breathing techniques that help patients achieve their breathing targets.

Freespira can reduce or eliminate symptoms in just 28 days because each session gives users the feedback, they need to achieve weekly, escalating targets for breathing rate and exhaled CO<sub>2</sub>. Freespira is extremely efficient: it takes just 28 days to complete; each session lasts just 17-minutes; and it's possible for users to train in any convenient location since the system is portable. Guiding users through three sections (warm-up, training, and practice) solidifies the necessary skills to reduce or eliminate panic disorder symptoms.

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## Clinical Data

The breathing protocols used in the Freespira program have been studied in four peer-reviewed clinical studies to determine the efficacy of a drug-free, remote, digital therapeutic that trains patients to regulate respiratory rate and CO<sub>2</sub> levels.

The first study established what would become the Freespira clinical protocol. The study assessed the efficacy of two 17-minute breathing regulation sessions per day, designed to normalize CO<sub>2</sub> levels, for 28 days. Thirty-seven patients with a diagnosis of panic disorder were randomly assigned to receive either breathing training (20 patients) or to be in a wait-list control group (17 patients). After the diagnostic interview, the clinician administered the Panic Disorder Severity Scale (PDSS), which was repeated post-treatment and at 2-month and 12-month follow up. In addition, at each of these time periods, respiratory data (exhaled CO<sub>2</sub> and RR) were obtained during standardized, supervised periods of extended quiet sitting and a voluntary hyperventilation test. The patients in the wait list group were assessed at the start and end of the waitlist period and were then treated with the therapy in the same manner as the treatment group.

In a second study based on the same protocol, 41 patients with a principal diagnosis of panic disorder were randomized to receive the breathing regulation therapy (21 patients) or Cognitive Training, a type of psychotherapy (20 patients). Patients in both groups completed about 64% of the specified 52 homework assignments. Overall, etCO<sub>2</sub> increased and respiratory rate decreased in the treatment group, but not in the Cognitive Training group. Psychological measures improved equally in both groups. However, the exhaled CO<sub>2</sub> measure was found to be a powerful mediator of change in panic symptom severity in patients in the treatment group, but not for patients in the CT group. Exhaled CO<sub>2</sub> was unidirectionally related to changes in symptom appraisal. There were no adverse events reported. These findings suggest that changes in etCO<sub>2</sub> are directly responsible for some of the changes in panic symptom severity.

These studies, in combination, reported that 62% of patients were panic attack free at 2-month follow-up and 68% of patients were panic attack free one-year post treatment. 93% demonstrated clinically significant improvement in the number or severity of panic attacks.



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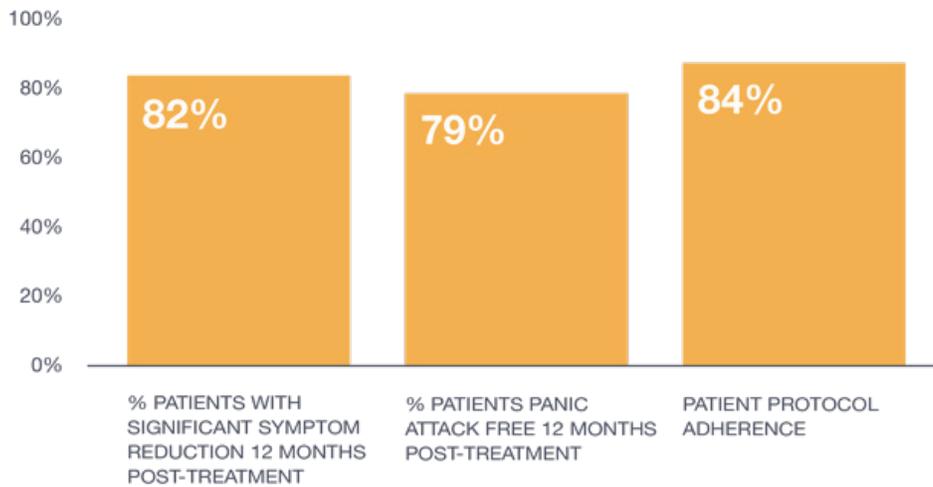
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<sup>11</sup> Meuret, A. E., Wilhelm, F. H., Ritz, T., & Roth, W. T. (2008). Feedback of end-tidal pCO<sub>2</sub> as a therapeutic approach for panic disorder. *Journal of psychiatric research*, 42(7), 560–568. <https://doi.org/10.1016/j.jpsychires.2007.06.005>

<sup>12</sup> Meuret A.E., Rosenfield D., Hofmann S.G., Suvak, M.K., Roth, W.T. (2009). Changes in respiration mediate changes in fear of bodily sensations in panic disorder. *Journal of Psychiatric Research*, 43: 634-41

## MULTI-CENTER PANIC DISORDER CLINICAL TRIAL STUDY

Institute of Living  
A Division of Hartford Hospital



A benchmarking study<sup>13</sup>, conducted by Dr. David Tolin, offered the Freespira treatment to 69 patients treated in multiple anxiety clinics. The purpose of the trial was to validate that individuals seeking treatment for their panic attacks have the same results as those in a formal research environment utilizing the practice-ready Freespira system. Freespira treatment was offered to patients at five different clinic locations across the country. These patients were demographically diverse and averaged a 10-year history of panic disorder. Patients followed the standard Freespira protocol: Two 17-minute breathing regulation sessions per day, for 28 days, supported by weekly check-in visits at the clinic.

Tolin's results, in clinical practice, mirrored the results from the earlier academic clinical trials: 85% of participants completing the Freespira treatment had clinically significant improvement at the end of the 28-days, and 82% were improved one year after treatment ended. 70 % of participants were in remission (no longer meeting criteria for a panic disorder diagnosis) a full year post-treatment. Functional impairment in work, school, and social and family life decreased from moderate to mild post- treatment and decreased further at six months post-treatment. No significant side effects or adverse events were reported.

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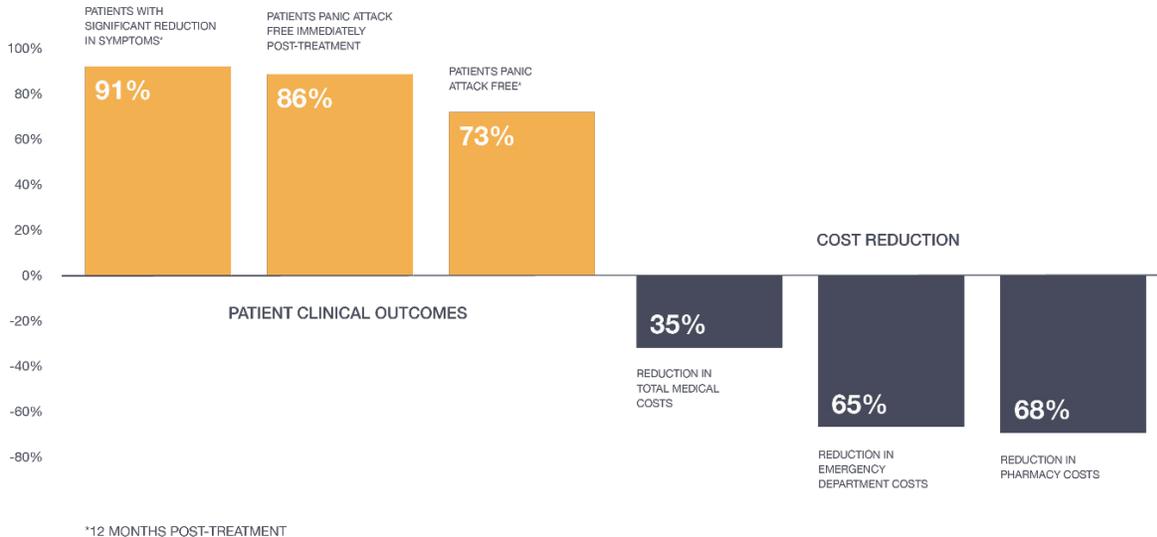
Numerous peer-reviewed clinical studies have demonstrated the efficacy of a drug-free, remote, digital therapeutic that trains patients to regulate respiratory rate and CO2 levels.

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<sup>13</sup> Tolin, D.F., et al. (2017), A Multisite Benchmarking Trial of Capnometry Guided Respiratory Intervention for Panic Disorder in Naturalistic Treatment Settings, *Journal of Applied Psychophysiology and Biofeedback*, 42(1): 51-58.

# Better Outcomes, Lower Costs

## HIGHMARK HEALTH ECONOMIC STUDY



VOL:0123456789 | 3 APPLIED PSYCHOPHYSIOLOGY AND BIOFEEDBACK [HTTPS://DOI.ORG/10.1007/S10484-020-09465-0](https://doi.org/10.1007/s10484-020-09465-0), EVALUATING THE IMPACT OF FREESPIRA ON PANIC DISORDER PATIENTS' HEALTH OUTCOMES AND HEALTHCARE COSTS WITHIN THE ALLEGHENY HEALTH NETWORK, ALICIA KAPLAN - ANTHONY P. MANNARINO - P. V. NICKELL.

A fourth study<sup>14</sup>, reporting results of the Highmark Health / Allegheny Health Network VITAL Quality Improvement Program (QIP), measured both the efficacy of the therapy as well as its impact on health care costs. Following a claims analysis that documented significantly greater medical costs for individuals with panic disorder compared to matched controls, Highmark Health, a Blue Cross Blue Shield plan, funded a program providing Freespira to members through the VITAL program.

The study, conducted at the Allegheny Health Network, measured cost reductions following Freespira in patients treated for panic attacks and panic disorder, as well as clinical outcomes, adherence and patient satisfaction. A series of 52 patients were enrolled and 44 completed Freespira. This study found that 68% of treated patients were in remission one-year post-treatment and 91% of treated patients had significant symptom reduction one-year post-treatment. Any-reason medical costs declined by 35% for the year after treatment for participating patients. Pharmaceutical costs were reduced by 68% and Emergency Department costs were reduced by 65%. After completing the program, 90% of participants would recommend or definitely recommend Freespira in a patient satisfaction survey.

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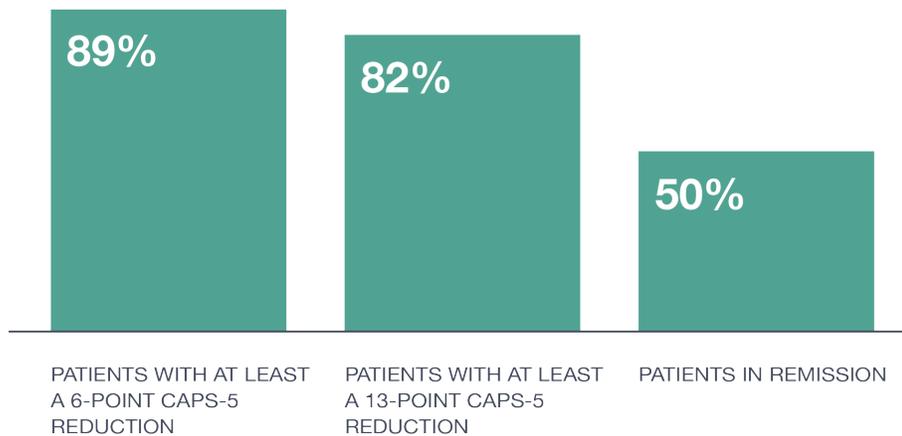
<sup>14</sup> Kaplan, A., Mannarino, A.P. & Nickell, P.V. Evaluating the Impact of Freespira on Panic Disorder Patients' Health Outcomes and Healthcare Costs within the Allegheny Health Network. Appl Psychophysiol Biofeedback 45, 175–181 (2020). <https://doi.org/10.1007/s10484-020-09465-0>

Meanwhile, positive results from clinical trials at the VA Palo Alto Health Care System<sup>15</sup> demonstrated the efficacy of Freespira in treating PTSD symptoms. Results from this clinical research showed more than 80% of veterans and civilian participants achieved significant improvement, with 50% in remission PTSD symptoms six months post-treatment. Adherence rates, at 77%, were strong, particularly for a use-at-home treatment.

Across all of these studies, Freespira significantly reduced symptoms of panic attacks and PTSD symptoms. A significant number of patients in all studies reduced their symptoms to a level that no longer met the criteria for diagnosis. This benefit lasted well beyond the course of treatment, with patients studied at six months or one-year post-treatment demonstrating the same or better response. Patients continue to put their new skills into practice in their everyday lives, long after they returned the system.

A significant number of patients in all studies reduced their symptoms to a level that no longer met the criteria for diagnosis.

### PTSD CLINICAL TRIAL RESULTS 6 MONTHS POST-TREATMENT



<sup>15</sup> Ostacher MJ, Investigation of the Freespira System in the treatment of PTSD. Submitted for publication.

## CONCLUSION: WHY FREESPIRA?

As a health plan or employer, you care about the health of your workers or members. Healthy workers are productive workers and health plan members with effectively managed panic attacks or PTSD are less costly. These members are also less likely to develop other behavioral health comorbidities.

While there is a well-established treatment landscape for panic attacks and PTSD, millions of people continue to suffer severe symptoms of these conditions that impair their ability to work, socialize, travel and live life to the fullest. There is a gap in the marketplace for a product that is:

- Evidence-based
- Safe and effective
- Requires a short duration of treatment
- Provides long-lasting results
- Medication-free
- Reaches patients with unmet needs

While many patients with hard-to-treat symptoms of panic attacks and PTSD have failed on multiple treatments, new digital therapies can provide a new avenue to achieve remission from these paralyzing conditions. The key is a digital therapeutic that combines real time breathing regulation training with the human touch of coaches. This solution teaches patients skills to help them manage their condition independently after completing a single 28-day treatment. Freespira is a must-have “tool in the toolbox” for healthcare providers and payers.

The cost benefits of this long-lasting, medication-free digital therapy are significant. In addition to the studies of workplace impacts referenced above, the Highmark Blue Cross/Blue Shield study measured an average reduction in overall medical costs for the patient of \$2,380 in the first year following Freespira treatment. This was accompanied by a 65 percent reduction in emergency department costs and a 68 percent reduction in pharmacy costs. The takeaway for employers and health plans is that Freespira pays for itself in the first year.

Freespira is an FDA-cleared, well-studied digital therapeutic that provides relief for the vast majority of patients who struggle with PTSD and panic attacks. This can be measured both in short- and long-term health outcomes and in return on investment for health care payers.

In addition to helping payers reduce costs, Freespira adoption represents a significant commitment to innovative, home-based treatments that promote patient empowerment. Interrupting the cycle of chronic anxiety can improve productivity and absenteeism, while reducing the risk of developing other behavioral conditions. Most importantly, quality of life for individuals and their families can bloom again as these life-impairing symptoms resolve.

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## About Freespira, Inc.

Freespira, Inc. is the maker of Freespira, the only FDA-cleared digital therapeutic proven to significantly reduce or eliminate symptoms of panic attacks, panic disorder, and post-traumatic stress disorder (PTSD) in just 28 days by training users to normalize respiratory irregularities. Health plans, self-insured employers and the Veteran's Administration use the company's drug-free solutions to improve quality of life, reduce medical spend and support the appropriate use of valuable healthcare resources. Find out how at [www.freespira.com](http://www.freespira.com).

12020 113th Ave. NE | Suite 215 | Kirkland, WA 98034-6951

**800.735.8995** | [cs@freespira.com](mailto:cs@freespira.com)