Category

Best Startup

Product/Solution Name

Prism for PTSD™

Date of Approval

2023-03-17

Indications

Prism is a neurofeedback software device intended for relaxation and stress reduction through the use of EEG biofeedback.

The device is indicated as an adjunctive treatment of symptoms associated with posttraumatic stress disorder (PTSD), to be used under the direction of a healthcare professional, together with other pharmacological and/or non-pharmacological interventions.

Therapeutic Categories

Neurology

Attached Files:

- Prix Galien Additional Questions_FINAL.docx

Background information and need for solution/product

MARKET BACKGROUND

Post-traumatic stress disorder (PTSD) impacts nine million Americans, mostly women. Until recently, PTSD standard of care treatment primarily focused on two areas – pharmacotherapy and psychotherapy. These treatment modalities have proven effective for many patients, and yet, PTSD is a unique journey for every patient, each of whom needs specialized treatment plans to meet their needs.

Many pharmacotherapies result in adverse side effects, while psychotherapy – including prolonged exposure therapy, eye movement desensitization and reprocessing and trauma-focused cognitive behavioral therapy - can be particularly challenging as patients are required to relive their traumatic experiences. Additionally, patients living with PTSD can face stigma, prejudice and discrimination, which can deter them from seeking talk therapy treatment. As a result of the above, as many as 50 percent of patients prefer to avoid therapy, only exacerbating their medical condition.

These challenges are further compounded by the shortage of mental healthcare professionals across the United States. Despite the rising rates in mental disorders, the United States does not have enough mental health professionals to keep up with the demand. This crisis is most acute for the 163 million people living in federally designated mental health professional shortage areas, with the latest statistics demonstrating a need for over 8,200 mental healthcare practitioners to fill the gap.

NEUROSCIENCE BACKGROUND

PTSD and many other mental disorders have long been associated with hyper-reactivity of the amygdala and limbic system. This has been demonstrated extensively by multiple researchers and clinicians globally, yet no therapeutic modality makes use of this knowledge.

It was with the above understanding of the neurological mechanisms, along with her psychiatry background, that Professor Talma Hendler, MD, PhD, Professor of Neuroscience and Psychiatry at Tel Aviv University and Director of the Sagol Brain Institute at the Tel Aviv Souraski Medical Center, started her journey.

Prof. Hendler is an international leader in transferring psychiatric and neurological scientific research into clinical practice. She is the founding director of the Sagol Brain Institute, a leading research facility and advanced clinical service of brain mapping. She has won several prestigious, large-scale competitive grants from national and international funds including the Department of Defense, European Union 7th Framework Programme for Research, Horizon, National Institute of Mental Health and others.

Prof. Hendler began her journey by looking into existing technologies and how they can be leveraged in a novel way. Technologies used to monitor brain activity include electroencephalogram (EEG) and functional magnetic resonance imaging (fMRI). EEG is a low-cost modality that measures brain electrical activity on the scalp through a patient-worn cap with electrodes, however, EEG is not able to measure electrical activity in deep brain regions. On the other hand, fMRI scanners are used to measure blood oxygenation (known as BOLD signal) in deep-lying specific brain regions but are expensive and complex to operate.

It has been demonstrated in multiple studies that when patients with amygdala-related mental disorders, such as PTSD, are placed in an fMRI scanner and are trained through neurofeedback to downregulate their amygdala fMRI BOLD signal, they experience an alleviation in their symptoms. However, fMRIs are expensive, complex to operate, and are not readily available, and so are not used as a therapeutic modality.

Until GrayMatters Health (GMH) was founded, no company had used both EEG and fMRI in conjunction to build an FDA cleared therapeutic tool.

A NOVEL COMBINATION OF EXISTING TECHNOLOGIES

In 2013, following years of research Prof. Hendler used advanced statistical models to fuse EEG and fMRI data of specific brain regions, creating an EEG-fMRI Pattern (EFP) biomarker of brain regions associated with mental disorders. The first EFP developed was the amygdala-derived-EFP by fusing EEG with fMRI voxels from the amygdala. The amygdala-derived-EFP biomarker was then used to train PTSD patients to downregulate it, leading to clinically significant improvements. Seeing the opportunity of the technology to create a paradigm shift in mental disorder treatment, GMH was founded by Oded Kraft, Rani Cohen and Shai Attia in 2018.

In its initial years, the GMH team worked with Prof. Hendler to conduct deep technology due diligence,

and perform studies on the EFP technology to validate its efficacy and safety. After concluding six successful studies that were subsequently published, the EFP technology clinical safety, effectiveness, viability, and scalability, were validated as well as its ability to be adapted for a variety of mental disorders.

Recognizing the potential of Prism to bring a third option to mental healthcare, the GMH team conducted market research, meeting with leading mental healthcare research institutions and professionals, and even payors to determine the best approach – ultimately deciding to begin developing Prism for PTSD treatment.

Using the amygdala-derived-EFP technology at the core of a neurofeedback device, Prism for PTSD, offers clinicians a novel way to help their patients. Prism combines neuroscience knowledge with imaging, advanced statistics, machine learning, and psychology into a new, third, modality that augments pharmaco- and psychotherapy. This modality which builds on the sense of agency, invites the patient to take an active role in their treatment process and has a high safety profile with a low rate of mild adverse events.

Prism for PTSD can be used in any clinic large or small and leads to significant meaningful and robust clinical outcomes. Prism does not require a pill, rather scientifically provides the patient with a skill, all under the supervision of a healthcare professional. Considering the high prevalence of PTSD and the challenges patients face in accessing appropriate care, Prism offers an alternative treatment option that is accessible, scalable, and effective.

Three years after raising its Seed investment in February 2020, and after conducting its pivotal study throughout COVID-19, on March 21, 2023, the U.S. FDA granted GMH a 510(k) clearance to market Prism for PTSD, bringing a third treatment option to PTSD patients. Prism for PTSD is the first FDA-cleared, non-invasive, self-neuromodulation prescribed adjunct digital therapy for PTSD that conducts neurofeedback on GMH's proprietary amygdala-derived-EFP biomarker.

ABOUT THE COMPANY

GrayMatters Health was founded by Oded Kraft, Rani Cohen and Shai Attia in 2018.

Oded Kraft, CEO of GMH, has over 25 years of international experience in global high-tech innovation and business development of both startups and large corporates that focus on medical device innovation. Before establishing GrayMatters Health, Mr. Kraft worked in executive business development roles within Roche and GE Healthcare and has also served on the board of several medical device companies in the EU, Israel and the US. Mr. Kraft holds an MBA and a BSc in Electrical Engineering from Technion Institute of Technology in Haifa, Israel.

Rani Cohen, Chairman of GMH is a high-tech entrepreneur and ex-venture capitalist with extensive experience in various technology companies in Europe, Israel, and the United States. Throughout his career, he served as Chairman, Co-Founder, and Founder of numerous companies across the fields of clinical trials, education, software and finance. Mr. Cohen holds a B.Sc. in mathematics and computer science from the Hebrew University of Jerusalem and an MBA from Yale University.

Shai Attia, VP R&D at GMH, has over 25 years experience in the development and software engineering

of medical systems and devices. Prior to founding GMH, he worked at GE, Elscint, Afimilk, and MedicVision, driving company products through CE and FDA approvals. Mr. Attia he holds a B.Sc. in software engineering and MBA from the Technion Institute in Haifa, Israel.

Attached Files:

- Background Information Slides_FINAL.pdf

History of the development of the solution/product

CLINICAL BASIS FOR PRISM

There are thousands of published studies indicating the amygdala's role in mental health. The amygdala, the control center of the fight-flight-freeze response, has been clinically proven to play a significant role in PTSD. To date, no single drug, medical device or behavioral treatment focuses on the amygdala.

It has also been demonstrated in multiple studies that when patients with amygdala-related mental disorders, such as PTSD, are placed in an fMRI scanner and are trained through neurofeedback to downregulate their amygdala hemodynamic blood flow, they experience an alleviation in their symptoms.

THE NOVELTY OF PRISM FOR PTSD

Prof. Hendler's research focused on developing methods for leveraging fMRI amygdala data to process EEG signals in a real time neurofeedback system. Achieving this would transform EEG neurofeedback into a modality that is based on sub-cortical fMRI data, thus bringing the best of both worlds – the spatial resolution data from fMRI together with the low cost, ease of operation, and temporal resolution of the EEG. She has published multiple peer-reviewed studies, covering 500 patients in randomized controlled trials across multiple indications, all of which served as the basis for Prism and the EFP biomarker.

In 2014, a review published in NeuroImage introduced Prof. Hendler's concept of a novel imaging approach using fMRI-inspired EEG. This paper introduced the EFP (then defined as Electrical FingerPrint, and now as EEG-fMRI-Pattern), the core of Prism's technology, which is calculated by identifying EEG features that correlate the activation level of specific brain processes associated with mental disorders as seen in fMRI. The EFP was developed by first performing a series of simultaneous acquisitions of EEG and fMRI under specific psychological paradigms aimed at improving Signal-to-Noise ratio (SNR), and then fusing the datasets with proprietary advanced statistical and machine learning models.

In 2016, Prof. Hendler published research in Biological Psychiatry and in PLOS One, applying this model to self-regulation training and neurofeedback settings. Additional papers were published on the use of the technology for the treatment of fibromyalgia.

Finally, in 2019 she published two studies in Nature Human Behavior Journal. The first demonstrated how an EFP of the amygdala could guide neurofeedback for building stress resilience. While the second examined a process-based framework for precise neuromodulation, showcasing self-modulation of brain activity as a promising tool by which neuroscientific knowledge could be

translated into actionable, psychiatric interventions. Later on, further studies were published demonstrating how the EFP neurofeedback approach can be used to treat PTSD patients.

The above studies provided the initial clinical basis for how the EFP technology, and an interactive audio/visual interface could be applied to create a new PTSD treatment modality.

TECHNOLOGICAL DEVELOPMENT OF PRISM

Moving forward in 2020, designing Prism for PTSD, the company team, including software, electrical, neuroscience, UI/UX experts, artists designing the interactive interface and score, and algorithm engineers, leveraged the existing amygdala-derived-EFP and added some critical best practice elements. The development process included multiple iterations informed by interviews with customers, providers, and payers.

The result was Prism for PTSD, a software device that interfaces with an off-the-shelf EEG and is installed on a laptop that is connected to a monitor. Prism software reads the EEG signal and uses the amygdala-derived-EFP biomarker to compute the EFP signal in real time. The level of the EFP signal controls the activity and noise of a virtual scene presented to the patient on the monitor. Throughout the therapy session, the HCP can view the patient's performance on the laptop. Therapy includes an initial set of 15, 30-minute-long sessions, spread over two months, and booster sessions later on as needed.

A simple setup, along with easy-to-follow operating instructions, made Prism ready to be easily installed in both large and small clinics. Prism is designed to be operated by non-MDs, thus lowering operating costs at the site. The first Prism installations took place at the height of the COVID-19 pandemic, at the end of 2020, in sites in the USA and Israel. Due to COVID, at times, installation and training were performed remotely over Zoom requiring less than three hours of training. Despite these conditions, provider teams testified fast ramp up and comfort of patients.

Clinic workflow is critical for the success of products in daily use. In an iterative process of customer interviews, the team was able to simplify the workflow of Prism. Following this change, Prism therapy session setup now takes about five minutes, leaving the majority of the session for active therapy.

The GMH team also created an interactive 2D audio/visual interface that could respond to Prism's EFP, it showcases a virtual scene of a reception room in which avatars are huddled around a reception desk and shout. As the patient practices different mental strategies, Prism for PTSD reads the EEG signal, uses it to compute the amygdala-derived-EFP, and uses that value to change what is happening in the user interface (i.e., reception room). As patients find the mental strategy that lowers the biomarker, the avatars sit, and the reception room becomes quieter. Think of it as placing a mirror in front of this specific brain activity. Over the course of the 15 sessions, patients practice this new skill and can improve with time.

The GMH team also collected data from past studies and used it to develop an updated version of the EFP feedback system. This resulted in better neuromodulation and improved response from the interactive loop. Further to this, the team programmed Prism to collect deidentified data during sessions with the aim of developing treatment predictors, patient management tools and treatment personalization. The company also created cloud software to contain all treatment sessions including

EFP data, EEG data and post-session questionnaire responses. This allows GMH to manage and own a unique high-volume EEG and psychiatric questionnaire database, associated with mental disorders along with a longitudinal assessment of treatment.

Following the development of Prism for PTSD, by the end of 2020, a clinical trial was initiated at five sites in Israel and in the USA, including NYU Langone under the direction of Prof. Charlie Marmar, one of the prominent KOLs in mental health and especially PTSD globally. The study ended by June 2022 and included 79 patients with chronic PTSD, at least one year since experiencing trauma and with stable medication regimen to exclude confounders. The study demonstrated a high rate of symptom improvement in nearly 70 percent of the study population with some cohorts at nearly 90 percent, a low rate of adverse event, and a low attrition rate. The trial yielded positive feedback from all participants and requests from patients to continue the treatment beyond the end of the trial.

Attached Files:

- Development and clinical evidence Slides_FINAL.pdf

Why this solution/product is innovative, the broad implications for future research, and/or how it will improve the human condition

Prism for PTSD is the first FDA-cleared non-invasive, self-neuromodulation, prescribed, adjunct digital therapy for PTSD. Prism brings together multiple, different disciplines including psychiatry, advanced statistics and machine learning, the arts and music, big data, and UI/UX, creating a comprehensive, accessible, scalable, and efficacious therapy targeting specific brain processes, with little to no side effects. While other treatment methods offer behavioral or biological approaches, Prism for PTSD offers both methods simultaneously by training patients to lower their own amygdala-derived-EFP-biomarker. Additionally, as an adjunct therapy, patients can maintain existing treatment regimens and clinicians can use Prism to augment treatment responses. In addition to using the amygdala-derived-EFP for PTSD treatment as cleared by the FDA, the company is now using the same EFP for developing treatments of other disorders (e.g. Borderline Personality Disorder, General Anxiety Disorder) and is developing additional EFPs (e.g. of the reward system) to treat other disorders (e.g. Substance Use Disorder, Major Depressive Disorder). Prism is also designed to generate large volumes of data, which will be used for patient and therapy prediction.

A THIRD OPTION FOR PTSD TREATMENT

Studies indicate that people with PTSD have increased amygdala activity in response to arousing stimuli, as well as reduced activity in parts of the frontal lobe that are responsible for regulating emotional responses. The limbic network, which includes the amygdala, mediates the emotional processing in the brain and plays a key role in many mental disorders. Until Prism for PTSD, no drug, medical device, or behavioral treatment directly targeted amygdala hyperactivity and limbic dysregulation nor utilized knowledge of underlying mechanisms of brain activity.

Before Prism for PTSD, EEG and fMRI, which offer two very different measurements of real-time brain activity, held promise but were ultimately too expensive and cumbersome to operate, and were never combined to produce a therapeutic tool. Prism uses advanced statistical models to convert an EEG signal measured in real time to an amygdala derived EFP biomarker. Through this, Prism remains accessible, affordable, portable and scalable.

AN ACTIVE ROLE FOR THE PATIENT

Prism for PTSD encourages patients to take an active role in their treatment journeys, empowering them to develop personalized skills to lower their emotional responses that can be utilized outside of the treatment setting. Whether a memory, emotion, or experience, patients use this emotional response to get the shouting avatars on the screen to sit down and lower their voices. As patients engage with Prism's interactive audio/visual interface, data from the amygdala-derived-EFP changes the virtual scene in response to their self-neuromodulation techniques. Like placing a mirror in front of a patient's brain activity, Prism for PTSD utilizes this biomarker to guide treatment and help patients gain control over this brain activity associated with PTSD.

In a treatment journey that is typically lonely and stigmatized, Prism for PTSD makes PTSD treatment as personalized as it can be while giving patients control of their journey. For example, one patient might find that thinking of a happy childhood memory helps lower their biomarker. Another patient might begin counting numbers and reach the same result. Crucially, Prism for PTSD, unlike other therapies, is not trauma-focused and patients are not continually exposed to their original trauma which helps drive low attrition rates.

ADDRESSING CAPACITY CHALLENGES

With the limited capacity of mental healthcare professionals today, and long waiting periods for patients, Prism is designed with operational simplicity to fit any mental healthcare clinic. As a prescription device offered in a mental healthcare practice, Prism requires minimal training and can be operated by non-MDs, using only EEG. Any psychologist, clinician, or clinical social worker at a large or small-scale clinic can offer patients Prism therapy. For clinics, Prism is a cost-sensitive treatment modality, made possible through the product's cost structure and the business models offered by the company, lowering operational costs and training time.

FUTURE DATA APPLICATIONS

Over time, deidentified data collected from Prism for PTSD sessions will be used to evolve the product and provide a holistic solution for PTSD. Using this data, we will be able to provide therapy predictions, optimize treatments and manage outcomes. As an example, we can determine which patients will benefit from additional or fewer initial sessions or a booster session.

Prism was built and designed as a platform. For now, only Prism for PTSD is cleared by FDA. In time, following expanded FDA clearance of Prism software to focus on other mental disorders, including Major Depressive Disorder or Attention Deficit Hyperactivity Disorder (ADHD), GMH will be able to simply install a software add on at the clinics. This way providers will be able to treat greater populations in need. The company is currently conducting a clinical study at McLean Hospital (Harvard University's largest psychiatric hospital) evaluating Prism for Depression. This product is using the reward-system-EFP (computed using fMRI data of the ventral striatum, nucleus accumbens and more) training patients with anhedonic depression to upregulate it, feasibility results are promising. The company is conducting further studies on Borderline Personality Disorder and ADHD.

VALIDATED CLINIAL OUTCOMES

In the multi-center clinical trial study, Prism for PTSD displayed a low rate of adverse events and a low attrition with patients experiencing few side effects during treatment. In addition, patients saw improvements in symptoms and gave positive feedback. The clinical results of the FDA study bear economical implication since they demonstrate a significant reduction in patients' CAPS-5 (PTSD severity) scores. These reductions in PTSD severity, when converted to healthcare costs could lead to $3000 to $7000 savings annually per patient. This saving means less spending by providers, payers, and patients, and importantly could mean less hospitalizations and health complications for patients. This also means less side effects and possibly less complications with comorbid conditions to PTSD.

GrayMatters has started selling Prism for PTSD to a select number of outpatient and private mental health clinics in the USA. It will expand its sales in early 2024.

Attached Files:

- Product innovation slides FINAL.pdf

Please provide appropriate references (ie Pubmed links)

https://pubmed.ncbi.nlm.nih.gov/24246494/ (NeuroImage)

https://pubmed.ncbi.nlm.nih.gov/30932053/ (Nature Human Behavior Jan 2019)
https://pubmed.ncbi.nlm.nih.gov/30988481/ (Nature Human Behavior April 2019)

https://pubmed.ncbi.nlm.nih.gov/27163677/ (PLoS One)

https://pubmed.ncbi.nlm.nih.gov/26996601/ (Biological Psychiatry)

CLP001 (publication in progress)