REVIEW ARTICLE

Virtual Reality Therapy Could be a Promising Alternative for Anxiety - A Review

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ABSTRACT

Anxiety disorders are the major mental illnesses globally, characterized by a persistent and variable clinical course. These disorders probably have a severe impact on a person's ability to function personally, socially, and professionally. A person suffering from such disorders could affect the standard of living. Anxiety disorders are classified within the vague category of neurotic illnesses. General disorders such as apprehension, fearfulness, restlessness, and agoraphobia are among the current categories of anxiety disorders. Anxiety is advantageous from an evolutionary standpoint since it promotes survival by motivating individuals to avoid hazardous environments. The frequency of symptoms associated with anxiety that are associated with each other is around 2 to 4% in the general population, and it may rise up to 20% with non-psychotic conditions. Then present systematic review aims to assess virtual reality therapy's (VRT) effectiveness in treating anxiety disorders. Our aim is to highlight the existing research to ascertain the effectiveness of VRT in alleviating symptoms of anxiety as well as its possible advantages and constraints in comparison to conventional therapeutic approaches. The review will further explore the fundamental mechanics of VRT and pinpoint any lacuna in the existing literature that necessitates more attention. Furthermore, these reviews are significant because they provide insightful information about how VRT could be used to treat anxiety and evaluate the effectiveness of VRT as a therapeutic intervention.

Keywords: Anxiety, Neurosis, Melancholy, Pathophysiology, Virtual reality therapy.

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INTRODUCTION

Anxiety is a common human characteristic to feel unease. Anxiety is a symptom of several mental illnesses, including anxiety, phobias, and panic attacks. Individuals commonly encounter apprehension, which frequently manifests in physical manifestations such as breathlessness, lightheadedness, perspiration, tachycardia, and trembling.[1] People with anxiety disorders usually experience substantial changes in their everyday and social behavior, frequently leading them to purposefully avoid certain situations and objects.[2] Restlessness is the serious reaction to a perceived danger and psychological pressure. Typical anxiety originates from fear and fulfills an important role in ensuring survival. When a patient encounters a perilous circumstance, worry stimulates the fight-or-flight reaction.[3] In reaction to such events, the body undergoes many physiological changes, including enhanced cardiovascular circulation to the heart and muscles. This event enables the body to acquire the essential energy and vigor required to confront life-threatening circumstances, such as evading a hostile animal or defending against an assailant.[4] Anxiety can facilitate an individual's adaptation to commonplace stresses by incentivizing them to engage in preparation, practice, and rehearsal. It can even induce an individual to approach potentially hazardous circumstances with a suitable level of prudence. The majority of mental health disorders are anxiety disorders, affecting about one-third of people in the United States (US) at some point in their lives.[5] Long-lasting anxiety might become ingrained and start to feel customary to individuals experiencing it. Anxiety disorders frequently go undiagnosed or untreated due to several factors. Additionally, they can be linked to the ideation of self-harm and actual suicide endeavors.[6] Additional conditions frequently accompanied by noticeable anxiety include post-traumatic stress disorder (PTSD), adjustment problems, and acute stress disorder. Many times, traumatic or stressful situations trigger these illnesses.[7,8]

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Virtual reality therapy (VRT) has demonstrated encouraging outcomes in the management of anxiety disorders. VRT enables users to immerse themselves in computer-generated surroundings that may be customized to target their unique anxiety triggers. This technology creates a secure and regulated setting for exposure treatment.[9] VRT enables individuals to gradually approach anxiety-inducing circumstances, providing a controlled and secure setting for them to face their concerns. Individuals can acquire coping skills and enhance their self-assurance in effectively managing their anxiety through this. VRT environments may be tailored to accommodate the unique requirements of persons with various anxiety disorders. For instance, those diagnosed with social anxiety disorder can engage in simulated social encounters inside a virtual environment. In contrast, individuals diagnosed with agoraphobia can mimic leaving their residences in a controlled environment.[10] VRT offers a fully immersive experience that enhances patients' sense of presence and engagement during therapy. This attention can facilitate the cultivation of a heightened feeling of agency in individuals, enabling them to exert better control over their anxiety and enhance their overall state of well-being.[11] VRT has the advantage of being an economical alternative to conventional in-person counseling by eliminating travel expenses and enabling more frequent sessions.[12] This can enhance the accessibility of therapy for persons who lack the means to participate in conventional therapy sessions. VRT can be utilized with CBT to increase the effectiveness of treatment by adopting a complete strategy. [13] Engaging in this activity can assist individuals in cultivating a diverse set of coping mechanisms and enhancing their overall mental well-being. VRT can potentially be a formidable tool in treating anxiety disorders due to its ability to create a secure and regulated setting for exposure therapy, its ability to customize surroundings, its immersive experience, its cost-effectiveness, and its adaptability when combined with other therapeutic approaches. This systematic review aims to assess the efficacy of VRT in the treatment of anxiety disorders.[14] The evaluation will examine recent studies to determine whether VR treatment is beneficial in reducing anxiety symptoms, as well as any potential benefits and drawbacks when compared to traditional therapeutic methods. The objective is to offer important insights into the possible utilization of VRT to treat anxiety disorders while guiding upcoming studies and clinical uses.

METHODOLOGY

The review was conducted strictly according to the PRISMA 2020 principles. The bibliographic study was conducted by utilizing the databases of PubMed, Psycnet, and Study Gate. The search was performed using a specific set of search phrases. VRT and Social Anxiety Disorder. VRT and social phobia; VRT and performance anxiety; VRT and Pilot study on anxiety.

Pathophysiology

The exact mechanism behind the development of anxiety remains elusive. The occurrence of anxiety in young individuals is prevalent. Regarding the physiological processes associated with anxiety, many neurotransmitter systems have been involved in one or more of the modulatory stages.[15] Usually, there is a rise in noradrenergic system activity and a fall in serotonergic system activity is believed to be implicated. When a hazardous signal enters an individual's brain, it is processed context-dependent through a sensory-neuronal circuit. This information is ultimately sent to the hypothalamus.[16] This hormonal feedback process links two brain regions with the adrenal gland, a small organ atop the kidney.[17] The hypothalamic-pituitary-adrenal (HPA) axis controls the reaction of the body to stress and plays an important role in anxiety. When external cues trigger the hypothalamus to secrete corticotrophin-releasing factor (CRF), the neurochemical aspect of the HPA signaling associated with fear or anxiety is initiated.[18] CRF synthesis activates the proximal pituitary gland for the secretion of ACTH (Adrenocorticotrophin-releasing hormone), which increases the release. The adrenal cortex produces glucocorticoids, such as cortisol, when it detects an elevation of ACTH in the bloodstream.[19] When glucocorticoids connect to their receptors in the pituitary and hypothalamus, a negative feedback loop is created that restricts future CRF and ACTH generation. Neurochemical interactions within the HPA system are responsible for the development of fearfulness, apprehension, or restlessness due to imbalances.[20] Figure 1 illustrates the HPA axis and the control of cortisol.

The brain's amygdala is responsible for behavioral and cognitive responses. The amygdala, a cluster of nuclei located inside the medial temporal lobes of the complex vertebrate brain, is crucial in generating anxious feelings. The amygdala receives sensory input from the thalamus. The amygdala integrates these inputs with cortisol processing before initiating efferent signals that trigger the danger response.[21]

The neurotransmitter 5-hydroxy tryptamine is a monoamine. Neurons that are serotonergic are mostly located in the dorsal and median raphe nuclei in the brainstem. Presynaptic nerve terminals release 5-HT into the extracellular space, where it is primarily eliminated *via* neurotransmitter reuptake, which is made possible by the 5-HT transporter.[22] The receptors for postsynaptic stimulation and those that are presynaptic self-receptors are present in 5-HT receptors. The regulation

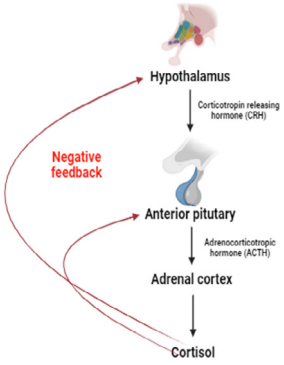

Figure 1: HPA axis and control of cortisol[20]

of serotonergic neuronal activity mostly depends on 5-HT autoreceptors, which play a crucial role in self-inhibition.[23] The activation of inhibitory 5-HT autoreceptors regulates the firing of 5-HT neurons and ensures the balance of the serotonergic system. 5-HT functions via binding to 5-HT receptors, encompassing the 5-HT1 to 5-HT7 families, each consisting of many subtypes. The effects of 5-HT are contingent upon the specific cell type and subtype of the receptor it stimulates.[24] Mounting evidence indicates that the serotonergic system is involved in somatic complaints. TPH (tryptophan hydroxylase) initiates the serotonin pathway by catalyzing serotonin synthesis. TPH-1 and TPH-2 are the two types of TPH enzymes found in mammals.[25] The vesicular monoamine transporter (VMAT) facilitates the transportation of 5-HT molecules from the cytoplasm to small synaptic vesicles. VMAT1 and VMAT2 are VMAT proteins found in mammals. VMAT1 is specifically situated in neuroendocrine cells, whereas VMAT2 is universally present in all serotoninergic neurons within the CNS.[26] The SERT protein facilitates the movement of 5-HT from the synapse. The enzyme MAO facilitates the oxidative deamination of 5-HT and breaks it down. Illustrates the process of synthesizing, releasing, and reuptaking serotonin and its impact on the postsynaptic receptor.[27]

The GABA-A receptor is a pentamer composed of five subunits, forming a passage that helps the chloride and bicarbonate ion to pass through,[28] Activation of γ-aminobutyric acid necessitates a minimum of two molecules. The GABA-A receptor has a wide range of apparent affinity for GABA, from low to high micromolar concentrations, similar to other ligand-gated receptor channels.[29] The subunit composition, particularly the a-b subunit dimers, significantly affects this value as they form the binding site for GABA agonists. An altered excitatory and inhibitory activity balance leads to anxiolysis, drowsiness, amnesia, and ataxia. Activation of the GABAergic system leads to a decrease in apprehension, fearfulness, anxious disorder and, excessive reactivity, and even convulsions.[30,31] These pharmacological conditions indicate that the suppression of neurotransmission has a role in developing brain disorders. Anxiety disorders, epilepsy, and schizophrenia are all characterized by deficiencies in GABAergic neurotransmission.[32] The first step in treating anxious states is to focus on enhancing inhibitory control, specifically by targeting the central nervous system's GABA receptor type A because anxious states are typically associated with increased neuronal activity in areas that process emotions.[33,34] Illustrates the release of GABA and its effect on GABA receptor

Current Pharmacotherapy Used in Anxiety Disorder

Anxiety disorders encompass a collection of mental health illnesses distinguished by an abundance and enduring presence of apprehension, anxiety, or uneasiness. Pharmacotherapy is commonly employed alongside psychotherapy to address symptoms associated with anxiety disorders effectively. Below is a concise overview of the present pharmacological options made for the treatment of mental disorders.[35]

Benzodiazepines

Benzodiazepines are a category of pharmaceuticals that function as depressants of the CNS. They attach to the GABA-A receptor, intensifying the suppressive impacts of GABA, leading to a reduction in symptoms of anxiety.[35] Lorazepam is a rapidly-acting benzodiazepine that has a high bioavailability of 95%. The compound has a high degree of protein binding, with around 95% coupled to proteins. Additionally, it has a half-life of 12 to 14 hours. Lorazepam undergoes hepatic metabolism and is eliminated by renal excretion. Adults are advised to take a 0.5 to 2 mg dosage orally thrice daily.[36] Alprazolam is a benzodiazepine that has a brief duration of action and a bioavailability of 90%. The compound exhibits significant protein binding, with around 90% bound to proteins. Its half-life, or how long it takes for the body to excrete half of the chemical, is between 11 and 14 hours. Alprazolam undergoes hepatic metabolism and is eliminated by urinary and fecal excretion. The suggested dosage for adults is 0.25 to 0.5 mg, used orally three times daily.[37] Clonazepam is a benzodiazepine that has a lengthy duration of action and a bioavailability of 90%. The compound exhibits significant protein binding, with around 80% bound to proteins. Its elimination half-life ranges from 18 to 50 hours. Clonazepam undergoes hepatic metabolism and is eliminated by urinary and fecal excretion. Adults should take 0.125 to 0.25 mg orally twice daily as advised.[38]

Selective serotonin reuptake inhibitors

Selective serotonin reuptake inhibitors (SSRIs) are a kind of antidepressant medication that specifically block the reabsorption of serotonin, resulting in elevated levels of 5-HT in the brain. SSRIs are efficacious in the management of symptoms associated with anxiety disorders.[39] Fluoxetine is an SSRI with a prolonged duration of action and a bioavailability of 90%. It has a high degree of protein binding, with 95% of the drug bound to proteins. Additionally, The duration of its half-life is 24 hours. Fluoxetine undergoes hepatic metabolism and is eliminated by urinary excretion. The prescribed dosage for adults is 20 to 60 mg, administered orally once a day.[40] Sertraline is an SSRI) that has a prolonged duration of action and a bioavailability of 40%. The drug has high protein binding, with 95% coupled to proteins. Additionally, the duration of its half-life is 26 hours. Sertraline undergoes hepatic metabolism and is eliminated by renal excretion. Adults are advised to take a single oral dosage of 50 to 200 mg daily.[41] Paroxetine is an SSRI that has a lengthy duration of action and a bioavailability of 90%. The compound has a high degree of protein binding, with approximately 95% binding to proteins. Its elimination half-life is 21 hours. Paroxetine undergoes hepatic metabolism and is eliminated by renal excretion. The suggested dosage for adults is 20 to 60 mg, administered orally once a day.[42]

Serotonin-norepinephrine reuptake inhibitors[43-44]

Serotonin-norepinephrine reuptake inhibitors (SNRIs) is used for the treatment of depression that specifically block the reabsorption of that specifically inhibit 5-HT and

Noradrenaline, resulting in elevated levels of these chemical messengers. SNRIs are efficacious in alleviating symptoms of anxiety disorders. Venlafaxine is a highly bioavailable long acting SNRI). Venlafaxine undergoes hepatic metabolism and is eliminated by renal excretion. The suggested dosage for adults is 75 to 375 mg, taken orally once daily.[43] Duloxetine is a prolonged-release SNRI) that has a bioavailability of 90%. The compound has a high degree of protein binding, with around 95% coupled to proteins. Additionally, it has a half-life of 12 hours. Duloxetine undergoes hepatic metabolism and is eliminated by renal excretion. Adults should take a dosage of 60 mg orally twice daily as advised. [44]

Buspirone

Buspirone is a pharmacological agent used to treat apprehension disorders. It belongs to the class of non-benzodiazepine anxiolytic drugs and functions by acting as a serotonin partial agonist. It is efficacious in controlling symptoms of anxiety disorders. Buspirone is a pharmacological agent with prolonged action duration and a bioavailability of 80%. The compound has a high degree of protein binding, with around 95% attached to proteins. Its half-life is relatively short, lasting between 2 to 3 hours. Buspirone undergoes hepatic metabolism and is eliminated by renal excretion. The suggested dosage for adults is 15 to 60 mg, administered orally twice daily.[45]

Pregabalin

Pregabalin is used to treat convulsions that is also efficacious in treating the symptoms of anxiety disorders. Pregabalin is a pharmacological agent that has a prolonged duration of action and a bioavailability of 90%. It exhibits a significant degree of protein binding, with approximately 50% of the drug bound to proteins. The drug's half-life ranges from 6 to 17 hours. Pregabalin undergoes hepatic metabolism and is eliminated by renal excretion. Adults are advised to take 150 to 600 mg orally twice daily.[46]

Effectiveness of VRT in anxiety

VRT has emerged as a promising alternative to traditional CBT for treating anxiety disorders. Numerous clinical experiments have been carried out to assess VR therapy's viability and effectiveness for treating anxiety disorders.[47]

For this research, a group of 18 persons diagnosed with social anxiety disorder (SAD) underwent a course of six weekly sessions of virtual reality exposure treatment (VRET) in combination with CBT. The VRET sessions exposed individuals to virtual social scenarios, including public speaking and social interactions. The study furthermore discovered that VRET was well-tolerated and welcomed by the subjects.[48] Rothbaum *et al*. (2014) conducted pilot research where 12 persons diagnosed with panic disorder underwent six weekly sessions of VRET in conjunction with (CBT). The VRET sessions comprised exposure to virtual scenarios that induce fear, such as simulating aircraft flights and being in densely populated areas. The findings demonstrated noteworthy decreases in panic symptoms, as assessed by the panic disorder severity scale (PDSS), compared to a control group placed on a waitlist. The study furthermore discovered that (VRET) was well-tolerated and welcomed by the subjects.[49] In a single pilot research done by Carl *et al*., 2016, the objective was to assess the efficacy of VRET for post-traumatic stress disorder. In this study, a group of 16 persons diagnosed with post-traumatic stress disorder (PTSD) underwent a treatment regimen consisting of eight weekly sessions (VRET) in conjunction with (CBT). The VRET sessions entailed exposure to simulated traumatic experiences, such as a vehicle accident and a military scene. The findings demonstrated substantial decreases in _ (PTSD) symptoms, as assessed by the PTSD Checklist (PCL), in comparison to a control group that was placed on a waiting list. The study furthermore discovered that (VRET) was well-tolerated and welcomed by the subjects.[50] The pilot research on VRET for obsessive-compulsive disorder (OCD) was undertaken by Ko *et al*. in 2018. Twelve patients diagnosed with (OCD) underwent a treatment regimen consisting of eight weekly sessions of (VRET) in conjunction with (CBT). The VRET sessions involved exposing individuals to virtual settings that were polluted, as well as engaging in obsessive behaviors. The findings demonstrated substantial decreases in symptoms of OCD, as assessed using the Yale-Brown obsessive-compulsive scale (Y-BOCS), in comparison to a control group that was placed on a waiting list. The investigation moreover discovered that VRET was well-tolerated and embraced by the individuals.[51] Carl *et al*., 2019 conducted a pilot research on the use of VRET for generalized anxiety disorder GAD. Within this research, a group of 18 persons diagnosed with (GAD) underwent a treatment plan consisting of eight weekly sessions of (VRET) in conjunction with (CBT). The VRET sessions involved exposing individuals to simulated anxiety-inducing scenarios, such as public speaking and time management. The findings demonstrated substantial decreases in symptoms of GAD), as assessed by the scale (GAD-7), in comparison to a control group that was on a waiting list. The study furthermore discovered that (VRET) was well-tolerated and welcomed by the subjects.[52] The research done by Rothbaum *et al*. (2010) examined the efficacy of virtual reality exposure therapy in treating individuals with PTSD. The study comprised a cohort of 34 individuals diagnosed with post-traumatic stress disorder (PTSD) who were allocated randomly to either VRT or conventional exposure therapy. The findings indicated that both interventions yielded comparable efficacy in mitigating symptoms of PTSD, with no notable disparities observed between the two cohorts.[53] Powers *et al*. (2013) examined the efficacy of virtual reality therapy in treating social anxiety disorder. The research encompassed a cohort of 50 individuals diagnosed with social anxiety disorder, who were allocated randomly to either receive virtual reality therapy or be placed in a waiting control group. The findings indicated that VR treatment exhibited a notable superiority over the waitlist control group in diminishing symptoms of social anxiety.[54]

Riva *et al*. (2016) conducted a study to examine the efficacy of VRT in treating acrophobia. The study encompassed 36

individuals diagnosed with acrophobia, who were selected at random to either undergo VRT or be placed in a waiting control group. The findings demonstrated that VR treatment had notably superior efficacy compared to the waitlist control group in mitigating acrophobia symptoms.[55] Kessler *et al*. (2019) determine the accuracy of VRT in treating panic disorder. The research encompassed a cohort of 102 individuals diagnosed with panic disorder, who were allocated at random to either receive virtual reality therapy or be placed in a waiting control group. The findings demonstrated that VR treatment had notably superior efficacy compared to the waitlist control group in mitigating symptoms of panic disorder.[56] Hofmann *et al*. (2011) performed a random experiment to evaluate the efficacy of (VRET) with standard exposure therapy (ET) for treating spider phobia. The study had 59 participants, and the findings indicated that both (VRET) and (ET) effectively diminished symptoms associated with spider phobia. Nevertheless, it was shown that VRET was well-received and caused less discomfort for participants than ET.[57-59] Rothbaum *et al*. (2015) conducted a randomized study to assess the efficacy of (VRET) for individuals with (PTSD). The study had 101 individuals, and the findings demonstrated that VRET effectively decreased PTSD symptoms in comparison to a waiting control group.[60] Riva *et al*. (2016) assessed the efficacy of (VRET) for treating obsessive- (OCD).[61] A sample of 70 population was selected and demonstrated a substantial reduction in OCD symptoms with the use of VRET in comparison to a control group that was placed on a waiting.[62]

CONCLUSION

The World Health Organization (WHO) reported that anxiety are prevailing the mental health globally, impacting almost 264 million populations in 2017. The incidence of anxiety during 12 months differs significantly between nations and cultures, with rates ranging from 3.4% in Asia to 20.8% in Africa, respectively. The estimated prevalence of anxiety in adults in the US is around 18.1%. Although anxiety problems are widespread, a significant number of persons do not actively pursue or obtain therapy. Only 36.9% of persons in the US who have anxiety disorders seek therapy, and merely 22.8% obtain treatment that meets the minimum requirements. While the present medication for anxiety may be helpful for specific individuals, many limits emphasize the necessity for alternative or complementary methods to address anxiety symptoms. Furthermore, the present medication may induce adverse effects such as nausea, dizziness, sleeplessness, and sexual dysfunction. The current medication for anxiety is subject to several limitations. However, (VRT) presents a potential alternative that effectively tackles many constraints. VRT is an efficacious, secure, economical, and easily accessible technique. The advancement and increased accessibility of VRT technology hold the potential to profoundly transform the management of anxiety disorders and enhance the outcomes for persons affected by these ailments. VRT has demonstrated the potential to mitigate symptoms of anxiety; however, further investigation is necessary to ascertain its long-term efficacy and durability.

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