Review

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Virtual Reality for Anxiety in Alcohol Use Disorder: Myths, Risks, and Realities

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Posted Date: 26 July 2024

doi: 10.20944/preprints202407.2121.v1

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Abstract: Background: Virtual Reality (VR) is an emerging tool in the management of anxiety, one of the most disturbing symptoms of Alcohol Use Disorder (AUD), which often leads to relapse. Still, patients with Alcohol Use Disorder frequently have a history of Acute Symptomatic Seizures, and they are subsequently excluded from studies using VR because of the hypothesized fear of inducing photosensitive seizures. The first part of this narrative review explores the pathophysiological mechanisms of seizures associated with AUD, specifically acute symptomatic seizures. In contrast, the second part explores virtual reality's safe use in seizure-prone individuals, highlighting that the current state-of-the-art is based on a biased perception and old epidemiological data from studies conducted on photosensitive seizures in the late 90s. VR exposure has yet to be reported as triggering seizures within known pharmacovigilance databases. **Significance:** The implications weigh heavily on VR research currently associated with this significant adverse event. Further studies are necessary to address the risk of seizures triggered by VR in patients predisposed to developing seizures, like alcohol use disorder patients with a history of acute symptomatic seizures. Such research is essential to ensure that the potential benefits of Virtual Reality as a tool for managing anxiety in individuals with alcohol use disorder and acute symptomatic seizures are not unduly restricted. Furthermore, AUD can also serve as an intervention model feasible to de-bias attitudes toward the current lack of evidence base concerning the significant adverse events of VR-induced seizures, therefore facilitating the clinical implementation of this unharnessed digital treatment interface.

Keywords: virtual reality exposure therapy; alcohol withdrawal syndrome; acute symptomatic seizures; anxiety; photosensitivity; kindling

1. Introduction

1.1. Alcohol Use Disorder and Acute Symptomatic Seizures

Alcohol consumption is a significant contributor to mortality and morbidity worldwide, affecting around 237 million men and 46 million women with alcohol use disorders. According to a 2016 report by the World Health Organization (WHO), approximately 3 million deaths can be attributed to alcohol, surpassing the mortality rates of tuberculosis, diabetes, and HIV/AIDS [1]. In

 doi:10.20944/preprints202407.2121.v1

DSM-4, "alcohol abuse" and "alcohol dependence" were classified as separate conditions. However, in DSM-5, these two terms were combined into a single condition called "alcohol use disorder" (AUD) [2]. This disorder is defined as a pattern of alcohol consumption that causes significant suffering or dysfunction, lasting for at least 12 months and meeting at least 2 out of 11 well-established criteria [2]. The legal criterion was removed, and a new criterion related to craving was added. Furthermore, a classification system was developed to categorize the condition associated with alcohol intake into three levels of severity: mild, characterized by 2-3 symptoms; moderate, characterized by 4-5 symptoms; and severe, characterized by six or more symptoms [2]. Alcohol withdrawal occurs when there is an abrupt reduction or interruption of alcohol intake after prolonged use of heavy amounts of alcohol. It occurs in about 8% of patients admitted to the hospital who have a condition linked to alcohol intake [3]. The occurrence of epileptic seizures or delirium tremens can complicate ethanol withdrawal [4].

While it remains uncertain whether Hippocrates authored the renowned "Sacred Disease" around 400 BC, what is clear is that he dismissed its demonic origins and instead attributed it to a brain pathology. Furthermore, he observed a correlation between alcohol consumption and the occurrence of epileptic seizures, a phenomenon also investigated by the Romans, who referred to it as Morbius convivial [5]. Around twenty-five percent of individuals who suffer from alcohol use disorder will also have a type of epileptic seizure [6]. Alcohol-related epileptic seizures are a common cause of acute symptomatic seizures. Research indicates that about one-third of all hospital cases involving epileptic seizures are linked to alcohol [7].

1.2. Virtual Reality's Use in Treating Anxiety Associated with Alcohol Use Disorder

Immersive virtual reality (VR) stands as a valuable tool in the treatment of anxiety disorders because it provides a safe and supervised way to expose patients to anxiogenic stimuli actively [8]. Anxiety is a common comorbidity in AUD and also serves as an intensifier for craving symptoms, subsequently contributing to relapse [9]. VR has emerged as a promising intervention for the management of anxiety disorders [10]. However, both AUD and VR exposure carry inherent risks of seizure activity. This article reviews the mechanisms underlying seizure risk in AUD and evaluates the potential for VR to induce seizures in this patient population. By integrating VR into treatment programs, therapists can provide innovative and practical tools to support recovery from alcohol addiction and manage related anxiety. However, while using virtual reality in patients with alcohol use disorder, it is worth evaluating the risk of triggering seizures, especially if the patient has a history of acute symptomatic seizures.

There appears to be a lack of direct research articles explicitly addressing the risk of triggering seizures using virtual reality not only to treat anxiety in alcohol use disorder patients but also to report seizures as adverse events. Most literature available tends to focus on virtual reality for anxiety treatment and general studies on alcohol use disorder, but not the overlap of all three. This highlights a significant gap in the current research literature.

2. Alcohol-Related Seizures

2.1. General Background of the Patient with Alcohol-Related Seizures

People with alcohol use disorder generally have a background of long-term alcohol abuse [11], most of them with a familial history and maybe a genetic predisposition not only to alcoholism but also to developing seizures [12,13]. Moreover, prolonged cerebral exposure to alcohol leads to changes at a receptoral level, chemical imbalances, and eventually alterations of neural networks, all of which, combined with frequently encountered head trauma, can lead to epilepsy. This raises the question of whether we can still use virtual reality in these situations. A thorough understanding of the mechanisms behind these neural alterations could clarify our concerns.

The patient with seizures related to alcohol consumption tends to abuse alcohol early in life, as shown by some studies [14]. Specifically, the patient begins using alcohol at a relatively young age, around 15 years old, progresses to alcohol abuse by the age of 23, and develops addiction by the age of 33 [14]. The phenotype of the patient experiencing seizures associated with alcohol use disorder is

 doi:10.20944/preprints202407.2121.v1

characterized by recurrent bouts of detoxification, a high prevalence of family history of alcohol-related disorders, and early onset of severe dependency syndrome [15,16].

2.2. Acute Symptomatic Seizures

Epileptic seizures that occur during ethanol withdrawal are categorized as acute symptomatic seizures, formerly referred to as provoked seizures [17]. It is a common problem that often happens with alcohol withdrawal. Seizures occur within a timeframe of 6 to 48 hours after a significant decrease in alcohol use or abrupt cessation, with the highest occurrence seen between 12 and 24 hours. In a research conducted in Germany, Reinecke et al. found that 74.1% of the 695 patients who had acute symptomatic seizures were attributed to ethanol withdrawal [18]. The percentage of patients with ethanol withdrawal who progress to epileptic seizures varies in studies from 5 to 30-40% [19,20].

Seizures reoccur in 5% of cases and can progress to status epilepticus, often challenging to treat. In rare instances, they can also develop SESA - Subacute encephalopathy with seizures of alcoholics, a neurological syndrome characterized by focal neurological deficits. Nedermayer first described this syndrome in 1981 [21]. The latter differs from ethanol withdrawal seizures by its focal aspect, as well as the time when they occur - either before or after the typical withdrawal phase. It refers to a specific type of non-convulsive status epilepticus that happens in individuals who regularly consume alcohol. It is characterized by encephalopathy, periodic lateralized discharges on the EEG, chronic ischemic microvascular changes on imaging studies, and, potentially, the reappearance of seizures when the anticonvulsant treatment is discontinued.

Patients with epileptic seizures related to alcohol have a significantly higher mortality risk compared to the overall population. This risk is four times greater in some studies than in the general population [22]. Further research conducted in Geneva and published in September 2023 by Sansone G et al. in the European Journal of Neurology revealed a mortality rate of 2.9% per year in the age range of 40- 64 years, which is 13 times higher than the overall mortality rate [23].

The mortality risk increases when taking into account the patient's medical history; the examiner considers the seizure to be the result of alcohol withdrawal without doing further examination of the patient. A retrospective study [24] was conducted on 140 patients who initially presented with an epileptic seizure, which was assumed to be related to withdrawal or alcohol consumption. However, further investigation revealed that other causes were responsible for 53.6% of cases, including traumatic brain injury, hemorrhagic/ischemic strokes, epilepsy, and metabolic disorders. European guidelines recommend brain imaging and EEG even in obvious cases of a first alcohol-related epileptic seizure [25].

3. Pathophysiological Processes

3.1. Alterations in Receptors Due to Long-Term Ethanol Use

Alcohol acts both as an agonist of GABA receptors and as an antagonist of NMDA receptors in some critical regions of the brain. At moderate levels in the bloodstream, it induces euphoria and behavioral hyperexcitability by enhancing the interaction between glutamate and NMDA receptors. At high levels, it leads to acute intoxication by potentiating the effects of GABA. When consumed in significant amounts daily and over a prolonged period, it activates GABA-A and GABA-B receptors that have an inhibitory role on the CNS and antagonizes NMDA receptors, which have an excitatory effect. To restore homeostasis, the body will try to increase the number of NDMAR-2B receptors and decrease the number of GABA-A receptors. Consequently, over an extended period, there is a persistent suppression of neuronal networks. Prolonged alcohol use results in the development of tolerance and physical addiction. When the level of alcohol declines or is suppressed, the NDMA receptors will escape from the ethanolic inhibition, and all the previously exposed changes will be unmasked, thus leading to a hyperactivity of the glutamatergic receptors, together with a reduction of the inhibitory GABA-ergic input. The result is a state of neuronal hyperexcitability, which explains the state of autonomic hyperactivity and the appearance of neuropsychiatric manifestations such as epileptic seizures and delirium tremens. The CIWA scale (Clinical Institute Withdrawal Assessment

 doi:10.20944/preprints202407.2121.v1

for Alcohol) is effective in measuring the severity of alcohol withdrawal syndrome. In contrast, the PAWSS scale (Prediction of Alcohol Withdrawal Severity Scale) has been validated for identifying patients who are at risk of experiencing complications from ethanol withdrawal. The pilot studies proved sensitivity, specificity, and positive and negative predictive values of PAWSS of 100% [26].

3.2. Experimental Models That Replicate Acute Symptomatic Seizures in Humans

Due to ethical considerations, the available empirical data about seizures during ethanol withdrawal is restricted to animal studies. These are useful in understanding the physiopathological mechanisms that underlie the epileptic seizures that occur during alcohol withdrawal - typically, these are generalized tonic-clonic seizures. Similarly, they are also produced in mice during ethanol withdrawal. In the studies conducted on rodent models, these seizures are triggered by the neural networks located in the brainstem, especially at the level of the inferior colliculus [27,28]. Similar mechanisms could contribute to the triggering of acute symptomatic seizures related to alcohol withdrawal in humans.

Studies on alcohol withdrawal seizures used as experimental models, either spontaneous seizure – a type challenging to monitor handling or audiogenic seizures. The latter are preferred because although they might be regarded as reflex seizures, they are easier to obtain and control. The induction of repeated episodes of withdrawal was associated with the occurrence of spontaneous epileptic seizures, which correlated with the duration of withdrawal and with the number of withdrawal episodes, also suggesting a decrease in the convulsive threshold in mice [29]. Spontaneous seizures could be considered closer to withdrawal-related seizures in humans since the latter does not appear to be triggered by an external stimulus. Nevertheless, studies related to withdrawal do not use the animal model of spontaneous seizures due to the difficulty of transposing data from the murine model to the human model. Although they occur in the same time interval since the last alcohol administration, the spontaneous seizures in the murine model are mainly myoclonic seizures, while in humans, they are predominantly tonic-clonic seizures, as found in the model of seizures induced by handling or audiogenic seizures.

3.3. Acute Symptomatic Seizures and the Kindling Phenomenon

The neurophysiological kindling phenomenon was first identified and documented in animals by Goddard et al. [30]. Subsequently, Ballenger and Post [31] proposed the kindling theory as a rationale for the progressive escalation of ethanol withdrawal symptoms. Recurring episodes of alcohol intoxication followed by withdrawal lead to a reduction in seizure threshold and an increase in the excitability of the central nervous system. These occurrences trigger the kindling process within subcortical structures, particularly in the limbic system, hypothalamus, and thalamus [31]. The intensity of withdrawal symptoms escalates progressively with each episode, resulting in epileptic seizures and delirium tremens. Initially, it was noted that the likelihood of experiencing seizures and delirium increases in correlation with the length of time a person abuses alcohol and the frequency of episodes of ethanol withdrawal [32]. Moreover, the intensity of epileptic seizures increases in correlation with the frequency of ethanol withdrawal episodes [33]. Before the definition of provoked/acute symptomatic seizures, Devetag et al. [34] studied seizures related to alcohol consumption and attempted to classify them. Additionally, they aimed to define Alcoholic Epilepsy as recurrent convulsive seizures that occur in patients without a history of epilepsy or other comorbidities with epileptogenic potential, such as head trauma/traumatic brain injury, infectious processes, cerebrovascular diseases, etc. These seizures should not be associated with alcohol withdrawal or excessive alcohol intake.

Patients who engage in excessive and long-term alcohol drinking (over ten years) are more susceptible to experiencing withdrawal-related seizures. On the other hand, Alcoholic Epilepsy often occurs after five years of using alcohol, even in limited amounts. Devetag hypothesized a potential genetic predisposition to trigger epileptic seizures, which he theorized to be associated with carbohydrate metabolism [34]. Research examining the link between alcohol consumption and the onset of epilepsy as a standalone condition has yielded conflicting findings.

 doi:10.20944/preprints202407.2121.v1

Some studies indicate a higher likelihood of epilepsy among individuals who engage in excessive and prolonged alcohol consumption [35,36], while others demonstrate no connection between the two [37]. However, Devetag's study showed that in Alcoholic Epilepsy, 65% of the seizures occurred in the morning; upon waking up, their occurrence may be due to the withdrawal induced by the sleep period, which, over time, causes a phenomenon of kindling through repeated, involuntary detoxifications.

A large number of experimental studies [38–40] have provided evidence that supports the kindling theory of seizures that occur during alcohol withdrawal. Neuronal networks involved in the propagation of the seizure across the brainstem include the cochlear nucleus, the superior olivary complex, and extends up to the inferior colliculus. During ethanol withdrawal in mice, there is a decrease in the inhibitory effect of GABA neurotransmitters in the inferior colliculus. This leads to an increase in neurons firing at this level [41]. Later, the neural network will expand, including the medial geniculate body, amygdala, and cortex. While these experimental findings in mice have provided insights into the processes underlying the development of epileptogenic neuronal networks associated with ethanol withdrawal, the data obtained are difficult to extrapolate to humans.

3.4. Changes in the Expression of Calcium Channels

The ethanol withdrawal-induced generalized tonic-clonic seizures studied on murine models exhibit comparable features to those observed in trials conducted on genetic epilepsy-prone (GEPR3) rats. Furthermore, it has been noted that during ethanol withdrawal, a seizure can produce changes in the expression of voltage-dependent calcium channels in the inferior colliculus. Specifically, there are changes in the expression of the mRNA subunit of the Cav2.1-a1 channel. These alterations occur three hours before and twenty-four hours after the onset of ethanol withdrawal symptoms, which is the period of highest susceptibility to epileptic seizures. Additionally, there is an increase in the current transmitted through these channels during this time [42].

3.5. Cerebral Atrophy

Seizures related to ethanol withdrawal, as those in temporal epilepsy, determine, in the acute and subacute stages, reversible cytotoxic edema in the temporal regions. Over time, they are also linked to hippocampal atrophy, mainly due to the loss of white matter volume [43]. Furthermore, the seizures that occur during ethanol withdrawal sometimes present with a condition called reversible posterior cerebral vasoconstriction syndrome. This syndrome causes vasogenic edema in the cerebellum, thalamus, and various regions of the white matter, namely the cortico-subcortical and deep regions of the white matter [44].

3.6. Genetic Mechanisms

Both alcohol use disorder and the complications of ethanol withdrawal seem to have a substantial genetic component, with the development of both conditions being impacted by the patient's gender. The genetic architecture is complex and still incompletely understood. A study published in 2022 in Molecular Psychiatry shows an overlap between genes involved in epilepsy and in neuronal excitability from epileptic seizures and a polygenic network associated with neural signaling pathways that contribute to the triggering of seizures related to ethanol withdrawal [45]. The genes linked to epileptic seizures and epilepsy are also present in murine models that are prone to seizures during ethanol withdrawal. The study identified several loci for significant quantitative traits (quantitative trait loci), targeting genes involved in the modulation of potassium channels and neuronal excitability, which are critical factors in understanding the genetic bases of ethanol withdrawal. Moreover, the study identified disturbances in the expression of genes involved in synaptic transmission, specifically those related to GABA-ergic and glutamatergic transmission, in the prefrontal cortex of mice. All this suggests a significant role that the genes involved in synaptic transmission play in ethanol withdrawal. Furthermore, the research establishes evidence linking these genes to the severity of ethanol withdrawal in people and the mechanisms related to addiction.

 doi:10.20944/preprints202407.2121.v1

This was achieved by the use of genetic association analysis in human patients, thus establishing a connection between studies conducted on animal models and alcohol-related disorders in human subjects. These results may help in better understanding why not all alcohol-dependent patients develop epileptic seizures.

3.7. Epilepsy and Alcohol Use Disorder

The prevalence of epilepsy among patients with alcohol use disorder appears to be three times higher than in the general population. Alcohol dependence correlates with poor control of seizures in patients with epilepsy. This is due to several factors, including the stimulating effect of alcohol on the brain, the withdrawal symptoms experienced when alcohol is stopped, the reduced absorption and increased breakdown of anticonvulsant medications caused by the induction of enzymes, the absence of therapeutic benefits, and the sleep disturbances commonly seen in chronic alcoholism. All of these factors contribute to the recurrence of epileptic seizures. A meta-analysis published in 2010 in Epilepsia found an essential association between alcohol use and unprovoked seizures or Epilepsy [46]. Furthermore, there seems to be a correlation between the amount of alcohol consumed, its long-term use, and the risk of developing unprovoked seizures or Epilepsy [46].

3.8. From Acute Symptomatic Seizures to Structural Epilepsy

The conceptual definition of Epilepsy from 2005 described it as a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures and by its neurobiological, cognitive, psychological, and social consequences [47]. Alcohol consumption is a well-known independent risk factor for the development of structural epilepsy, particularly in individuals with a history of head trauma [48]. This often happens due to repeated falls, loss of consciousness, involvement in physical assaults, road accidents, and similar situations. Neuroimaging investigations conducted in cases of head trauma often reveal cerebral contusions and subdural hematomas, which are associated with a significant likelihood of developing post-traumatic epilepsy [49].

Intracerebral hemorrhage and displacement of midline structures result in severe neuronal injury, including the disruption of neuronal networks, the development of gliosis, and the formation of epileptogenic foci [48].

Nevertheless, it seems that mild head traumas carry a greater likelihood of developing post-traumatic epilepsy compared to severe head traumas. However, the underlying processes responsible for this phenomenon have remained elusive till now. Wang et colleagues performed several animal model experiments and showed that a reduced level of neuronal autophagy, a crucial characteristic for maintaining cellular hemostasis, may have a significant impact on the development of post-traumatic epilepsy. This finding suggests that targeting neuronal autophagy might be a potential approach for developing preventative pharmacotherapeutics [50]. Cranial fractures, which determine brain injury through compression, are also associated with the risk of post-traumatic epilepsy, but somewhat less than in the aforementioned instances.

A 2016 meta-analysis revealed that those who regularly consume high quantities of alcohol (>30g/day) are at a heightened risk of experiencing subarachnoid hemorrhage [51]. Furthermore, for every 10g/day increase in alcohol consumption, the risk of subarachnoid hemorrhage rises by 12.1% [52]. Patients who regularly consume alcohol over a long period often experience problems with blood clotting due to liver dysfunction. This can lead to decreased platelet count (thrombocytopenia) and an imbalance between procoagulant and anticoagulant factors. Combined with impaired functioning of the blood vessel lining (endothelial dysfunction), these patients are more susceptible to cerebrovascular damage, particularly subarachnoid hemorrhage, intracerebral hemorrhage, and ischemic strokes. The latter is also influenced by a cardioembolic mechanism, namely atrial fibrillation linked with dilated cardiomyopathy caused by alcohol use. Furthermore, it often relates to high blood pressure and alcohol-induced vasospasm, which are risk factors for lacunar cerebral infarctions and atrial fibrillation [53].

4. Virtual Reality's Use and Seizure Risk

 doi:10.20944/preprints202407.2121.v1

In this part of the article, we will explore the relationship between VR as an important emerging tool in the management of anxiety and craving related to addiction and the potential risk of triggering seizures in patients with alcohol use disorder, especially those with a history of acute symptomatic seizures.

4.1. Reflex Seizures and Virtual Reality

Seizures triggered by different external stimuli, most often visual or by certain daily activities, are called reflex seizures [54] and are frequently associated with genetic epilepsy syndromes in the young population. EEG is a valuable tool to detect not only interictal and ictal epileptiform discharges but also the sensitivity of the brain to certain stimuli, especially when it comes to photic stimulation. Intermittent photic stimulation cannot affect EEG or induce a photo paroxysmal response, meaning spikes, spike, wave, or polyspike and wave complexes or slow waves, either bilateral or localized to the occipital region. This method of detecting photosensitivity is critical when it comes to making lifestyle recommendations for people who might present situational reflex seizures.

A better understanding of the brain's sensitivity to different visual stimuli could lead to establishing a protocol for VR software designed for people with seizures, where triggers like the most epileptogenic known frequencies (10-30Hz in humans), specific colors (like red or alternating red and blue) or particular patterns could be avoided. Fisher et al. (2022) describe in an updated review by the Epilepsy Foundation that provocative content like flashes, specifically those brighter than 20 candelas/m2 at 3-60 (mainly 15-20) Hz, occupying at least 10 to 25% of the visual field could be a risk for triggering seizures [55].

On the other hand, virtual reality stands out as an important potential tool for studying photosensitivity. For example, VR-Photosense software was developed to detect photo paroxysmal responses in real-time using a brain-computer interface with EEG and different scenarios that stimulate epileptogenic frequencies and color manipulation [56].

4.2. Virtual Reality in People with Epilepsy

As technology evolves, so is our current understanding and practice of using it to benefit patients. Recently, there has been a growing interest regarding the potential use of VR in treating associated anxiety in patients with epilepsy. This could be regarded as a controversy since, in general, most of the studies conducted using virtual reality excluded patients with photo paroxysmal response on EEG, photosensitive epilepsy, or some other type of Epilepsy based on the assumption that the virtual environment could trigger another seizure. Hence, this population can not benefit from integrating virtual reality for their specific needs. Moreover, the Oculus provider states as a safety warning the potential risk of triggering seizures in 1 in 4000 people, even in those without a history of seizures or epilepsy [57]. Still, this number refers to the approximate prevalence of photosensitive epilepsy in the general population, a number derived from epidemiological studies conducted after the 1950s, when this entity came to the attention of researchers with patients complaining of seizures after watching television [58].

After 1993, precautions were taken, and guidelines were developed to restrict flash rates and long-wavelength red [57]. Since then, and with the development of VR, no other guidelines addressing this issue have emerged, and all commercial products rely on the epidemiological data retrieved from the studies mentioned above. Nonetheless, interest has risen in readdressing this contraindication for virtual reality's use (Table 1).

Table 1. Articles discussing VR use in Epilepsy.

Title, authors, journal, and year of publication	Intervention	Population	Results or expected outcomes

 doi:10.20944/preprints202407.2121.v1

Concern of Photosensitive Seizures Evoked by 3D Video Displays or Virtual Reality Headsets in Children (Tychsen L, Thio LL. Eye and Brain 2020)	3D (binocular three-dimensional, stereoscopic) Movies or Games – on standard video displays or VR headsets	Children with epilepsy or Children with known PSE or PPR elicited during EEG recording	The medical literature does not support the notion that using VR headsets poses a risk for PSE.
Virtual Reality Therapy for People With Epilepsy and Related Anxiety: Protocol for a 3-Phase Pilot Clinical Trial (Gray HG et al. JMIR Res Protoc. 2023)	Participants Receiving VR-Exposure Therapy Treatment	Pilot study with 5 participants	Evaluate whether VR-ET is effective in decreasing anxiety in people with Epilepsy.

In the perspective article *Concern of Photosensitive Seizures Evoked by 3D Video Displays or Virtual Reality Headsets in Children* [59], the authors review the low risk of photic-induced seizures in children using VR headsets, even those with photosensitive epilepsy. This suggests that, generally, VR use does not pose a significant risk of triggering seizures. Moreover, in our view, interesting results could emerge from the study *VR-Therapy on People With Epilepsy and Related Anxiety* (AnxEpiVr) [60,61], which uses virtual reality to treat seizure-related anxiety in people diagnosed with epilepsy. This article highlights the need for personalized VR environments to avoid seizure triggers, focusing on epilepsy patients' anxiety. In phase 3 of this study, we will be able to see not only if virtual reality has an impact on the management of seizure anxiety in people with epilepsy but also if there will be adverse events like actually triggering a seizure while using the head-mounted display.

4.3. Virtual Reality in Alcohol Use Disorder Studies

Several studies have investigated the use of VR for alcohol use disorder either as a modality to lower cravings or manage comorbid anxiety. A study using VR as an add-on therapy to treatment, as usual, showed significant improvement in the levels of anxiety and alcohol craving treatment as usual, especially in patients with intense alcohol cravings, anxiety is a trigger for craving [62]. Studies also show a significant reduction in relapse rates in AUD patients. The use of VR in exposure therapy has shown promising results in enhancing self-efficacy and reducing the tendency for automatic drinking behaviors in individuals with AUD [63].

5. VR in Treating Anxiety in AUD and Seizure-Prone Individuals

A systematic review of the Adverse Effects of Virtual and Augmented Reality Interventions in Psychiatry, published in JMIR Mental Health in 2023 by Lundin RM et al., found cybersickness as the most frequent adverse effect and did not report any epileptic events [64]. Findings indicate that no conclusive evidence directly links VR use to an increased seizure risk in AUD patients. Conducting clinical trials to assess this intersection can provide concrete data and guidelines for safely incorporating VR into treatment plans for AUD patients.

5.1. Different Mechanisms between Acute Symptomatic Seizures and Photosensitive Seizures

We have examined the various mechanisms underlying acute symptomatic seizures associated with alcohol use disorder, from long-term receptoral changes to neural network alterations and the development of structural epilepsy. While these factors theoretically contribute to a lower seizure

 doi:10.20944/preprints202407.2121.v1

threshold, and we could also address the genetic predisposition to seizures, at the same time, photosensitive seizures have a different mechanism and also a different genetic background. Consequently, the assumption that virtual reality could trigger seizures, even in patients with alcohol use disorder and a history of acute symptomatic seizures, is not substantiated by current evidence and appears to be biased.

5.2. Adaptable Virtual Environments

VR offers nowadays highly customizable environments that can be adapted to individual patient needs and can reduce potential seizure triggers by avoiding rapid visual changes and intense stimuli while effectively addressing anxiety symptoms. Technology is evolving, and we are now capable of producing content that can filter epileptogenic flashes, modulate colors, and therefore, avoid events like the so-called Pokemon epidemic seizure effect from almost 30 years now of technological evolution that brought to the Emergency Departments in Japan, in 1997, 685 children with photosensitive seizures after watching a famous cartoon on TV [65,66].

5.3. Step-by-Step Desensitization

VR enables gradual and controlled exposure to anxiety-provoking stimuli, which is a cornerstone of effective anxiety treatment. This can be particularly beneficial for individuals with AUD, who often experience spikes in their anxiety during the withdrawal and recovery phases.

5.4. Screening for Adverse Effects and Safety Measures

Using strict monitoring protocols during VR sessions, we can quickly identify any side effects and adjust VR settings to keep patients safe. We can establish a standard for broader VR applications once we demonstrate that the same rigor for safety and patient care applies to AUD patients.

5.5. Holistic Treatment Approach

Integrating VR into a comprehensive treatment plan that includes medical management, psychological support, and lifestyle modifications can enhance overall outcomes for individuals with AUD and seizure risks. VR may serve as a bio-psycho-social interface to facilitate the synergy of the therapeutical continuum, starting from inpatient mild alcohol withdrawal management towards secondary craving exposure therapy within rehab facilities and bridge support groups within a vivid framework to promote adherence.

With AUD as a blueprint, we can argue for a paradigm shift in the way VR therapy is viewed for those experiencing a range of medical conditions. We can advocate for its safe and effective use and emphasize the need for future research in this field.

6. Conclusions

Seizures associated with alcohol use disorder are most often acute symptomatic seizures. Understanding these seizures extends to experimental models, primarily based on animal studies due to ethical constraints, in which we have investigated some of their most critical physiopathological mechanisms. Such research has contributed to the knowledge of kindling phenomena, where repeated alcohol withdrawal episodes reduce seizure threshold and increase CNS excitability. Additionally, genetic studies have begun to unravel the complex interplay between genetics and the risk of seizures during ethanol withdrawal, pointing towards a significant genetic component in alcohol use disorder and its complications.

We have discussed the fact that seizures observed in AUD patients are more commonly associated with withdrawal, and their mechanisms are different from those involved in photosensitive seizures. With proper precautions, VR could be a viable tool for anxiety treatment in alcohol use disorder patients. Future clinical trials should establish more explicit guidelines and safety protocols, adapting VR software environments to ensure they can be safely and effectively used in clinical settings. Adopting these practices can significantly change the paradigm of VR and

help overcome biases that continue to hold it back from realizing its true potential to enhance mental healthcare.

Albeit VR may represent a promising, safe, and effective intervention management tool for alleviating anxiety non-pharmacologically in AUD, as long as this current myth overshadows research protocols regarding the only VR-encountered major adverse event of triggering seizures, there is no place for researchers at the corporate-driven round-table conceptualizing the disruptive Metaverse, therefore necessitating further research.

Author Contributions: Conceptualization, M.A.G. and A.M.G.; methodology, M.A.G, A.M.G, C.T.; software, C.T.; validation, A.M.G., C.T., L.A.M., M.A., D.H., C.S., A.S.S., C.S., B.S.; formal analysis, C.T., L.A.M.; investigation, M.A.G, A.M.G, C.T..; resources, A.M.G, M.A.G, C.T.; data curation, C.T.; writing—original draft preparation A.M.G., M.A.G., C.T., A.S.S., L.A.M., B.V.S, C.S.; writing—review and editing, A.M.G., M.A.G., C.T., L.A.M, D.H., A.S.S.; visualization, M.A.G., A.M.G, C.T., D.H, C.S., B.S., A.S.S., L.A.M, M.A.; supervision, M.A.G., A.M.G, C.T., D.H, C.S., B.S., A.S.S., L.A.M, M.A..; project administration, A.M.G., L.A.M.; funding acquisition, L.A.M. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by the University of Medicine and Pharmacy „Grigore T. Popa Iași" PhD Scholarships for (M.-A.G: and A.-M.G.) and the Romanian Academy of Sciences, grant number GAR 56 (L.-A.M., M.-A.G., A.-M.G., C.-M.T., M.A.).

Institutional Review Board Statement: This narrative review involves no human participants, and ethical approval was not required. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Informed Consent Statement: This narrative review involves no human participants, so no informed consent was required.

Data Availability Statement: As a narrative review, research findings are based on published literature, and no new data was generated.

Acknowledgments: To the Editor and peer reviewers who acknowledged this paradigm shift.

Conflicts of Interest: The authors declared no potential conflicts of interest regarding this article's research, authorship, and publication. The funders were not involved in any way with the current state of the manuscript.

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