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Virtual Reality as an Adjunct to Ketamine Infusion Therapy Increases Patient Satisfaction in the Management of Chronic Pain and Depression: A Retrospective Pilot Study

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Abstract

The management of patients with concomitant chronic pain (CP) and Major Depressive Disorder (MDD) remains challenging for clinicians. Current chronic pharmacologic management is often unsuccessful, or has intolerable side effects to the patients. While not restricted to patients with chronic pain, these patients are often diagnosed with depression, presenting with symptoms such as poor mood, anhedonia, and altered cognitive processes. It is estimated that a substantial proportion of treated patients do not derive a substantive benefit from traditional pharmacological treatments for depression. The present study involved a retrospective review of cases, exploring the patient-reported satisfaction with and tolerability of a novel use of virtual reality (VR), coined KVR, as an adjunct to intravenous ketamine infusion therapies. Specifically, the ketamine-virtual reality protocol was employed as a potential adjunctive intervention for patients suffering from chronic pain and depression. Visual Analog Scores (VAS) associated with pain were significantly lower on the third than on the first assessment day. Montgomery-Åsberg Depression Rating Scale (MADRS) scores improved following infusion and across days (*i.e.*, sessions). Lastly, 2/3 of patients preferred the use of VR with their ketamine infusion. The results are considered in terms of implementing prospective studies to examine whether the combination therapies have a synergistic benefit and the nature and magnitude of clinically meaningful treatment effects, if any.

Keywords

Ketamine, Infusion Therapy, Virtual Reality, Chronic Pain, Depression

1. Introduction

More than 20% of adults in the United States report experiencing symptoms associated with chronic pain [1]. Unfortunately, effective treatments without severe side effects have proved elusive, as with the treatment of chronic pain associated with the widely reported opioid epidemic [2] [3]. Although opioids show limited long-term efficacy [4] [5], they continue to be widely prescribed, despite the high potential for addiction and overdose [4]. Thus, efficacious alternative treatments are worthy of consideration.

While much of the literature discusses dissociative experiences in terms of drug effects or psychopathology, it has been proposed that pain-related dissociative experiences are a biological adaption driven through frontal cortex inhibition of subcortical areas, including the anterior cingulate gyrus [6]. Pain signals emanating from the insula project to, among other areas, the anterior cingulate gyrus, and damage to this pathway can produce dissociative responses, including even laughter in the presence of pain [7]. Further, patients diagnosed with PTSD often present with both anxiety and dissociation [8]. As Defrin *et al.* [8] note, the two sets of symptoms appear to be related to different forms of emotional dysregulation, producing hyperresponsiveness and hyposensitivity to pain (see also, [9]). Dissociation is emotional, often accompanied by physical numbing and a sense of detachment, as well as a variety of atypical experiences [10]. Further, dissociation has been found to be related to pain hyposensitivity [8].

Depression is a clinical disorder that presents with a number of symptoms that may include poor mood, anhedonia (the inability to experience pleasure), alterations in sleep habits and appetite, and altered cognitive processes [10]. While traditional pharmacological treatments have included compounds that have an effect on serotonergic, noradrenergic, and/or dopaminergic signaling, it is estimated that approximately 20% of treated patients do not derive a substantive benefit from these treatments [11].

Antagonists of the N-methyl-D-aspartate receptor (NMDAR), such as ketamine, demonstrate considerable promise for the treatment of comorbid depression and chronic pain (NMDAR) [12] [13] [14]. Ketamine, an uncompetitive NMDAR antagonist, was approved by the FDA for induction and maintenance of anesthesia in 1970 and in 2018, the S-enantiomer of ketamine, esketamine, was approved for treatment-resistant depression (TRD) [15]. Although the FDA approval of esketamine is recent, racemic ketamine has been widely administered off-label for major depressive disorder (MDD) and chronic pain conditions for more than a decade [16] [17] [18].

The utility of selective serotonin reuptake inhibitor (SSRI) antidepressants is

limited by a delay in the onset of therapeutic activity that may be as long as three months [11] [19] [20] [21]. Conversely, ketamine exerts its therapeutic effect rapidly with some clinicians reporting rapid and robust alleviation of depression symptoms following a single administration [22]. For patients who have not responded favorably to traditional treatments, including those with suicidal ideation, ketamine can represent a potentially life-saving intervention, rapidly alleviating suicidal ideation in just hours [22].

Given reports such as those described above, ketamine has been administered off-label for MDD (major depressive disorder) and chronic pain conditions subsequent to first-line medication ineffectiveness or conventional treatment failure [17] [18].

Further, as a dissociative anesthetic, patient reports of the effects of ketamine have included reports of well-described out-of-body experiences, such as observing one's own body and its pain externally as a third-party observer [6].

The mechanism of ketamine's therapeutic activity is the subject of ongoing investigation, with research implicating numerous targets including NMDARs, AMPA receptors, μ-opioid receptors, GABA receptors, nicotinic acetylcholine receptors, adenosine receptors, eukaryotic elongation factor 2, glycogen synthase kinase-3, mTOR, BDNF, and TrkB [23]. Some of these hypothetical mechanisms are contradictory (e.g., both activation and inhibition of mTOR have been implicated in ketamine's antidepressant action) or based on experiments with methodological flaws or limitations. A leading hypothesis is that ketamine promotes release of glutamate in the prefrontal cortex via blockade of NMDARs expressed on GABAergic inhibitory interneurons, activating AMPA receptors and leading to enhanced BDNF signaling that promotes the growth of new dendritic spines, synapses, and other forms of neuroplasticity [24]. Research suggests the antidepressant effects may be independent of its antagonistic NMDAR action [25]. Studies have suggested activation of synaptic plasticity through the increase in brain-derived neurotrophic factor (BDNF), also associated with response to classical antidepressants, as well as glycogen synthase kinase-3 (GSK-3) inhibition, which has been suggested in animal studies to be necessary for rapid antidepressant effect via inhibition in the hippocampus and prefrontal cortex [25] [26] [27] [28]. Sub-anesthetic (<1 mg/kg) serial doses of IV ketamine have been demonstrated to be a safe and efficacious treatment in chronic pain disorders as well as rapid relief of depressive symptomatology in MDD/TRD [29].

As noted earlier, the customary pharmacological interventions for the treatment of depression are noted for a delay in the onset of therapeutic improvement [19] [20]. Affecting monoaminergic neurotransmitter systems, delays in therapeutic improvement may be as long as three months and the efficacy of these compounds is both variable and, in many cases, only minimal improvements in symptoms are seen [11] [21]. Given this, research has turned to alternative treatments such as the examination of ketamine, which has been investigated due to reports of rapid and efficacious antidepressant effects [22]. For patients who have not responded favorably to more traditional pharmacological

treatments, including those with suicidal ideation, ketamine offers a potentially viable alternative [22].

As a technology, the use of virtual reality (VR) in the clinical setting as an analgesic, anxiolytic, and distraction intervention during painful, uncomfortable, tedious, or anxiogenic procedures has rapidly been gaining popularity in the field of medicine. Until recently, costs and ease of administration were prohibitive, often costing thousands of dollars for the technology, and requiring wired tethering to a high-performance PC as well as external positional tracking sensors. Fortunately, the cost has declined significantly with systems available for as little as a few hundred USD for a modern stand-alone, inside-out tracked, head-mounted display (HMD) [30]. The technology holds considerable promise. For example, VR provides the participant with an immersive experience potentially across multiple sensory modalities in a three-dimensional environment, which has been used to distract from the medical setting and unpleasant or painful procedures. Technological advances have been accompanied by greater attention to the ergonomic form factors that affect the experience. Given this, ease of use by the patients and administering medical professionals has increased dramatically, as has the physical comfort of patients in clinical environments [30].

Research suggests that the multisensory experience provided by VR, providing simultaneous stimulation of visual, auditory and proprioception modalities, reduces processing of nociceptive stimuli [31]. Indeed, research employing fMRI to examine VR has revealed that among pain patients, the cortical region of the brain involved with attentional processes and the modulation of pain are more active. Conversely, activity in areas of the brain associated with the perception of pain is attenuated [32] [33]. Given such findings, it has been proposed that VR appears to alter the perception of pain through attentional, cognitive, and emotional domains.

The "gate theory" of attention, postulates that VR reduces the perception of pain by diverting attention away from the pain through other sensory stimulation [34]. VR may also increase patient adherence to therapy and increased satisfaction with the infusion process, by distracting from the psychoactive effects possible with ketamine. Though patients may report euphoria, some have reported anxiety, dysphoria, or other discomfort from the dissociative effects of ketamine. VR has been used to distract from the unpleasantness of the medical setting, which may be amplified under the psychotropic effects of ketamine administration. The immersive and multi-sensory nature of VR has demonstrated superiority to other forms of distraction, such as 2D television viewing, in several studies, including VR for chronic pain [30] [34]. In terms of anxiety related to ketamine infusion, one study found that environmental and ketamine-induced anxiety was associated with negative treatment responses in MDD, and even suggested the use of "audiovisual shielding of patients via headphones with music/video or virtual reality goggles" [35]. Thus, VR has the clinical potential to

act, not only as immersive distraction during painful or stressful procedures, but function as an anxiolytic and analgesic as well.

Owing to the fact that, like ketamine, the use of VR appears to be effective in a variety of treatments, consideration of the use of the combination of both in clinical settings may serve well in increasing well-being and ultimately in patient health outcomes. Further, the combination may very well produce synergistic effects that are greater than the use of each treatment approached separately. Lastly, this combination therapy may be useful for the amelioration of pain [18] [36] [37] [38] as well as other patient issues such as depression and anxiety [27] [39] [40] [41], and even in unexplained pain among individuals diagnosed with major depression [42].

The present study involved a retrospective review of cases, exploring the patient-reported satisfaction with and tolerability of a novel use of virtual reality (VR) as an adjunct to intravenous ketamine infusion therapies. Coined KVR, the virtual reality protocol was employed as a potential adjunctive intervention for patients suffering from chronic pain and depression. By review of current literature, the use of VR in the treatment of pain and depression with ketamine and the determination of whether this combination therapy would be tolerated and efficacious has not yet been described. Thus, a primary goal of the study was to ascertain whether further study is warranted and to inform further iterative development of the VR software and patient experience through patient feedback.

2. Method

2.1. Participants

The sample consisted of 18 patients recruited from Manhattan Restorative Health Sciences. Because VR may cause motion sickness in some users [43], patients were excluded with a history of motion sickness and vertigo and patients actively experiencing symptoms of nausea or vomiting. Patients with a history of seizures or epilepsy were also excluded to limit the potential risk of VR-induced seizures. Inclusion criteria included a clinical definition of chronic pain (ICD-11; MG30 codes) and a major depressive disorder [10] as part of patient screening. Therefore, the study consisted of data from 18 adult participants, 10 male and 8 female patients (M_{age} = 47.5, SD_{age} = 14.26).

2.2. Apparatus and Instruments

For the present study, a VR application called Visitations (Light Clinic, Brooklyn, NY) was developed for the unique requirements of patients undergoing ketamine assisted therapy. The application consists of 8 different procedurally generated, real-time rendered, 3D scenes ranging from natural landscapes to more abstract imagery inspired by Kluver form constants. The patients were allowed to self-select visual environments (see sample stimuli in **Figure 1**) at will through the use of a remote control. Ambient soundscapes accompanied the scenes on headphones and emphasized the use of binaural beats and brown or

pink noise accompanied the scenes. VR was administered using the Oculus Go headset (Meta, Menlo Park, CA) (Figure 2). The typical set up for the sessions is presented in Figure 3. The Oculus Go HMD (head-mounted display) is capable of delivering a 360-degree immersive experience of visual imagery and sound. This particular headset was chosen due to it being lightweight, inexpensive, and entirely self-contained and not needing external computers, cellphones, or wires compared to previous VR HMDs, and thus improved ease of use by study administrators and improved patient comfort. Headsets were disinfected between patients by wiping down with 10% ethanol solution.

Figure 1. Sample of VR imagery from the Visitations software, developed by David Lobser of Light Clinic.

Figure 2. Oculus Go headset (Meta, Menlo Park, CA).

Figure 3. Left, a patient receiving the KVR infusion set-up; right: a research staff member undergoing early iterative development of the therapy protocol.

For clinical depression, the Montgomery-Åsberg Depression Rating Scale (MADRS) was utilized. The scale is widely used, brief, and, noted for its sensitivity to change and high reliability, thus useful for cross-session comparisons [44].

Current pain levels within sessions were assessed using the Visual Analog Scale (VAS). Due to its simplicity and adaptability across settings, the instrument is widely used as a validated measure of chronic pain [45] [46] [47]. The participants rated the severity of their pain by marking a point on a 10-cm VAS (0 = no pain to a score of 10 = worst possible pain). The overall satisfaction and side effects, if any, during treatment were assessed using a questionnaire. All survey questions were taken from previously validated surveys.

2.3. Procedure

Participants were informed that the purpose of this open label study was to assess the utility of virtual reality and satisfaction with overall treatment during ketamine infusion in patients with a concomitant diagnosis of chronic pain and depression. After explaining the study intervention and end points, informed consent was obtained for each participant. First, all participants enrolled in the study protocol were pretreated with (1 mg IV midazolam). Following pretreatment, they were administered 3 infusions of IV ketamine on separate nonconsecutive days over one week. The treatment dose was determined at 0.5 mg/kg of ketamine delivered over a 40-minute period. For infusion day 1, participants were offered ketamine alone. In order to assess pre- and post-treatment effects on mood and pain, the 10-item MADRS and VAS pain scales were administered immediately prior to drug infusion and one-hour post-infusion. Doing so allowed for pre-drug effects as well as those post-infusion. After the treatment, all participants were asked to complete a survey in order to assess for the presence of any perceived side-effects and satisfaction with the treatment.

For day 2 of the infusion, the patients were offered an Oculus Go VR headset to use during the infusion. Participants chose from different VR scenarios as described earlier in the Apparatus & Instruments section with a handheld control. Consistent with day 1, MADRS and VAS scale were administered pre- and one-hour post-infusion. Additionally, patients completed the survey to assess for satisfaction with the treatment and any potential side effects.

For the final day of infusion (day 3), the patients were offered the choice to use VR headset. As before, VAS and MADRS scales were measured pre- and one-hour post-infusion. A similar satisfaction survey and screening for potential side-effects was administered post-infusion, as well as screening for potential side-effects.

3. Results

The VAS scores were examined using 2 (pre- vs. post-infusion) × 3 (days) within-subjects ANOVA. Examination of the resulting analysis revealed the following. A significant main effect of infusion period was found, $F(1, 34) = 54.86$, $p < 0.001$, $\eta_p^2 = 0.763$. Here, post-injection VAS scores ($M = 6.24$, $SD = 2.43$) were significantly lower than pre-injection VAS scores ($M = 6.24$, $SD = 2.43$). A main effect of days, $F(1, 34) = 4.43$, $p = 0.02$, $\eta_p^2 = 0.207$, was also detected but the interaction was non-significant. As seen in **Figure 4**, subsequent post hoc examination of the data revealed that VAS scores were significantly lower on the third ($M = 4.41$, $SD = 2.34$) than on the first ($M = 5.31$, $SD = 2.44$) assessment day, with scores on the second assessment day intermediate to but not significantly different than days one and three.

When the MADRS scores were considered, the following emerged. The relevant results are presented in **Figure 5**. First, when compared to pre-infusion ratings ($M = 26.06$, $SD = 7.58$), post-infusion MADRS scores declined significantly ($M = 9.50$, $SD = 5.79$), $F(1, 34) = 119.74$, $p < 0.001$, $\eta_p^2 = 0.876$. Similarly, when pre-infusion ratings were compared on day one versus day three, the resulting difference (Ms = 26.06 vs. 10.89) was significant, $F(1, 34) = 93.05$, $p < 0.001$, $\eta_p^2 = 0.846$. Thus, at least in terms of the available data, MADRS scores improved following infusion and across days (*i.e.*, sessions).

Patient satisfaction with the treatment process was explored using one-sample Kolmogorov-Smirnov tests. For all three sessions, the patients were highly satisfied with the experience, a result that was statistically significant (smallest $z = 2.59$) for each of the three sessions. In fact, the mean rated satisfaction for all three sessions exceeded 9.

Of the 18 patients, 12 preferred the ketamine injection with the use of VR. While this result is not significant, it is suggestive of potential additional treatment benefits derived from the inclusion of a VR experience supplementing drug treatment. Patient satisfaction levels with the VR component of treatment were somewhat lower for sessions two and three, with only the second session statistically significant (0.223, $p = 0.018$).

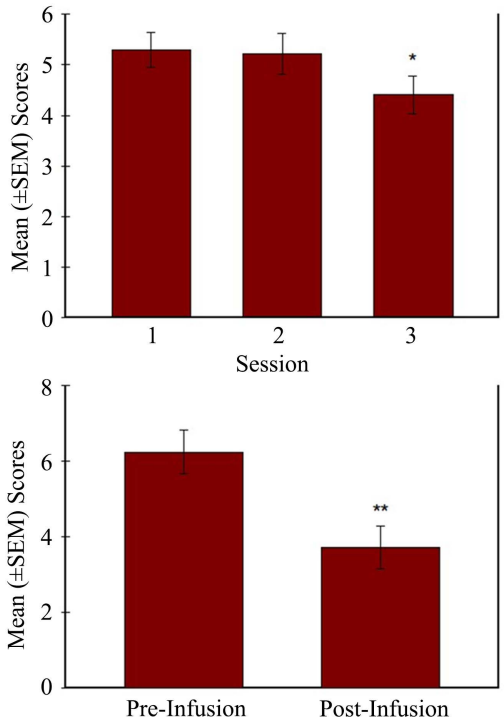

Figure 4. Results of perceived pain as measured with the Visual Analog Scale (VAS). *Significantly different from Session 1 and 2 ($p < 0.025$). **Significantly different from Pre-infusion VAS scores.

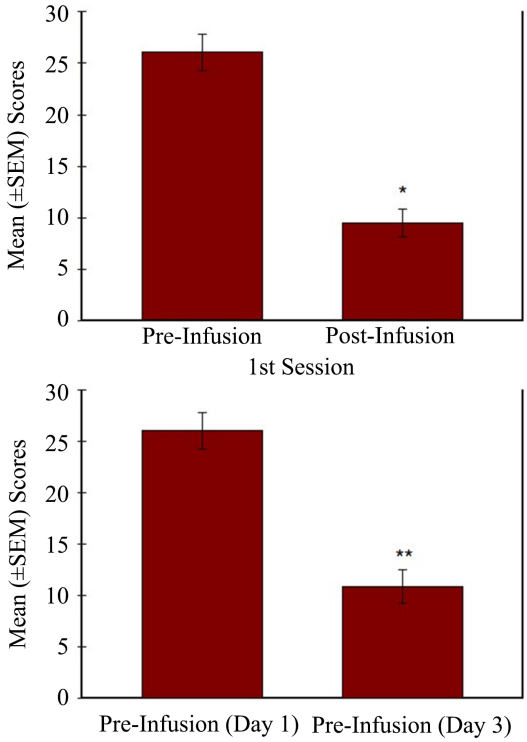

Figure 5. Results of the severity of depression as measured with the Montgomery-Asberg Rating Scale (MADRS). *Significantly different from Pre-infusion ($p < 0.001$). **Significantly different from Pre-infusion day 1 ($p < 0.001$).

Last, subjective patient feedback comments from the survey were used for iterative modification and improvement of the VR experience. Patient comments included the following:

"The most amazing medical procedure I've ever experienced;" "Has transformed my life;" "Almost miraculous;" "I wasn't concentrating on the effects of the drug or anxious… more immersed into the VR;" "My friend commented that he hasn't seen me this good in a long while;" "VR took edge of anxiety away; pretty good mood; gets you away from thinking."

When asked, "Why did you prefer KVR?" patients responded: "KVR acts as a guide; distracts from medication;" "with VR I was able to be distracted from sensations that would cause me anxiety;" "helps focus on setting to avoid my brain wandering to a bad place."

4. Discussion

While tentative, the results of the present investigation do lend support to the supposition that subanesthetic ketamine treatments with adjunctive VR therapy provide pain relief with concomitant rapid and efficacious antidepressant effects. As such, the results are in accord with those reported elsewhere [30] [48] [49] [50] [51] [52]. For individuals who continue a program similar to the one reported here, it may be possible to see a consistent reduction in perceived pain and in reported symptoms of depression. Such effects could in turn facilitate recovery efforts through changes in mindset that could well lead to greater social engagement and meaningful activities, and improvement in lifestyle choices. In turn, as an approach, such multi-faceted treatment strategies could very well facilitate the magnitude of physical and mental health recovery. However, although research reports regarding the use of VR for pain or procedural discomfort in the medical setting are encouraging [53] [54] [55] [56], many studies lack features such as the use of a control group for comparisons with VR [57] (but see also [30]).

Given the putative encouraging effects of ketamine on treatment resistant depression and pain, interest in the use of the drug and the S(+) enantiomer of ketamine (esketamine) has increased considerably [51] [58]. Esketamine (Spravato) is available as a nasal spray for unipolar and bipolar depression. Short-term efficacy as defined by a standardized mean difference (SMD) for TRD has been reported as 0.28 [59]. Nonetheless, the clinical usefulness of esketamine is still debatable [60] [61].

To reiterate, ketamine is an antagonist for N-methyl-D-aspartate (NMDA) glutamatergic receptors [51]. NMDA receptor function is essential for a variety of neurological functions [62]. Acting as a noncompetitive voltage-dependent channel blocker [62], ketamine presumably exerts some of its potentially clinical effects at low doses, with higher doses associated with psychotomimetic effects [63] and, eventually, anesthesia [64]. At low doses, ketamine exerts effects such as an antidepressant through protein synthesis and enhancement of excitatory

drive in corticolimbic brain regions [40] [65]. However, lacking a complete understanding of the exact mechanisms, it is prudent to proceed slowly until the positive effects can be weighed against any putative side effects [40]. Nonetheless, owing to the positive and often profound immediate and sustained clinical effects [66] [67] [68] [69], continued research associated with the post-synaptic NMDAR complex is warranted [70].

Turning towards a role for VR, there is evidence for a variety of therapeutic effects. For example, past research has demonstrated that as an effective, non-pharmacological treatment analgesic properties, VR is effective [57] [71] [72] and may be particularly useful for severe pain [72]. In a U.S. Army case study of 4 burn victim patients, a combination of VR and ketamine was found to have alleviated the perception of pain [73]. As noted earlier, a number of perhaps interrelated mechanisms for the effect have been proposed. One proposal appears promising; in any task that is highly immersive in nature, there is a concomitant reduction in sensory perception peripheral to the attentional demands at hand. VR, simultaneously impacting visual, auditory, and proprioceptive sensory modalities may very well create an immersive distraction capable of largely inhibiting the ability of the brain to process pain [74]. Lastly, the neurobiological substrates driving these effects on pain perception are an area of considerable investigation [33] [71] [75] [76] as well as anxiety and related disorders [77] [78], and depression [79].

5. Limitations

The present investigation was a pilot study with a retrospective design, with the study conducted in 2018, having been in development with the nascent VR technology since 2014. Therefore, the limitations included a small sample size, the concomitant consequence of low power as well as a research design that precluded the use of randomization. Indeed, the lack of randomization is commonly associated with a number of systematic biases [80]. In our study, the participants included a small subset of a larger patient population treated at a single medical facility. Further, it has been noted that in order to determine the maximum effects of ketamine, measurements should be included up to and including one day post-administration [81] [82]. Thus, the design used in the present study did not allow for comparison of the ketamine treatment alone versus the combination therapy or differentiation of the effects of either component alone. In addition, the design was deficient simply due to the absence of placebo control group.

Additional confounding factors can arise from the use of a broader chronic pain population with comorbid conditions, as different etiologies of pain or depression may respond differently to the combination therapy. The inclusion criteria for defining a depressed mood were more loosely defined, and the chronic pain conditions varied, including complex regional pain syndrome, degenerative and neuropathic spinal pain, musculoskeletal pain.

In addition, the participants were permitted to self-select from a variety of experiences that differed in terms of visual and audio components, or even adding music of their own choosing. Given this, it is possible that collectively the differences in visual and auditory stimuli may have affected the perception of satisfaction. For example, certain visual experiences (e.g., abstract geometric visuals) were more frequently associated with negative subjective open-ended comments.

6. Conclusion

Subsequent prospective studies can further explore whether there is an additive or synergistic benefit of the combination therapies and the nature and magnitude of clinically meaningful treatment effects if any. A placebo-controlled study differentiating between the individual components of the therapy versus the combination therapy, delineating specific patient populations (e.g., unipolar vs. bipolar depression, the presence of anxiety disorders), and using refined MADRS score cutoffs would be a worthwhile endeavor. Further, a study should be conducted in order to differentiate between the effects of the different VR experiences to ascertain if certain types of visuals, environmental settings, or auditory components are more conducive to measurable outcomes. Here, a systematic exploration of the effects of abstract imagery versus peaceful scenery auditory stimuli that include nature or ambient sounds versus music or even music of different types would be valuable in the assessment of clinical effects and whether certain types of visual and auditory stimuli maximize desired clinical outcomes. Last, it is worth including patient follow-ups to determine the length of treatment effect and whether the combination therapy persists longer than the ketamine administration alone.

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The VR application used in this research was "Visitations" by Light Clinic, and was developed by David Lobser.

Conflicts of Interest

The authors have no financial interest or stake in the facility where the research was conducted.

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