VIRTUAL REALITY AND PSYCHEDELICS FOR THE TREATMENT OF PSYCHIATRIC DISEASE: A SYSTEMATIC LITERATURE REVIEW

Federico J. Gómez-Busto, Mario I. Ortiz

Objective: Hallucinogenic substances or psychedelic drugs have been historically used by humans worldwide for centuries, and interest grows around them because of the therapeutic potential that they pose for mental disease. Virtual Reality (VR), has been highly developed and improved in the last decade, and it is also gaining importance due to their potential as therapeutic tools. In this article, the most recent and relevant information regarding the medical applications of both VR and psychedelics was highlighted, and diverse potential therapeutic uses were explored in hope to set the ground for further research on this topic.

Method: A systematic literature review using the PRISMA methods was conducted in PubMed, Medline, Embase, Cochrane Library, Scopus and Web of Science, including only peer-reviewed clinical trials or case studies written in English, that address the use of psychedelics and/or VR for the treatment of psychiatric disorders and that measure the success of the therapies. A final selection of 23 manuscripts were used in this systematic review.

Results: VR showed security and significant efficacy in the management of special cases of phobias (social, motion pain and spiders), eating disorder, post-traumatic stress disorder (PTSD), gambling disorder, preoperative anxiety and schizophrenia.

Conclusions: The hallucinogenic drugs evaluated exhibited positive effects in treatment of depressive and anxiety disorders, alcohol dependence and PTSD. More research is needed in order to test the effectiveness of these therapies (alone or together) in different mental illnesses and different populations.

Key words: psychedelic, hallucinogen, virtual reality, psychiatric disorders, psychiatry

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Introduction

Hallucinogenic substances, also known as psychedelic drugs, or simply psychedelics, have been historically used by humans worldwide for centuries, and have been mostly related to mysticism and religion, because of the psychotropic effects that they produce, which are referred to as mystical or transcendental experiences. Nowadays the properties of these mysterious substances have been increasingly studied, due to their potential use as a "catalyst" in cognitive therapy, that may reduce the months of therapy that are required for the treatment of depressive or anxious disorders, and because it has been observed that this kind of substances can also be used to treat drug addiction (Halberstadt, 2017). Virtual Reality (VR), sometimes referred as "virtual environments", a concept first presented by Sutherland (1965), has been highly developed and improved in the last decade, mostly because of its potential use for various disciplines such as architecture, arts and engineering, and also for its recreational use in the videogame industry, and more recently, in psychology, medicine and psychiatry because of the growing interest for its therapeutic use for the treatment of various pathologies, such as anxious and depressive disorders (Riva, Wiederhold, & Mantovani, 2019) as well as for the treatment of schizophrenia (Bekele, Bian, Peterman, Park, & Sarkar, 2017), for the management of pain and as part of the rehabilitation of patients post-stroke (Maier, Rubio Ballester, Duff, Duarte, & Vershure, 2019). Studies have been made regarding the potential of VR to mimic the transcendental or mystical experiences produced by psychedelics, with promising results (Glowacki et al., 2020), although almost no studies have been made regarding the synergetic effect of both VR and psychedelics, and the potential applications in health sciences, either for the treatment of mental pathology and medical therapy, for instance, the management of pain in a terminally ill patient with cancer. In this article, the most recent and relevant information regarding the medical applications of both VR and psychedelics was highlighted, and diverse potential therapeutic uses were explored in hope to set the ground for further research on this topic.

Background

Virtual reality definition

Virtual Environments (VE), Virtual Reality (VR),

Synthetic Experience, Virtual Worlds, Artificial Worlds or Artificial Reality are some of the most commonly used terms that refer to an interactive and immersive computer-mediated experience in which an individual perceives a simulated environment via the use of special human-computer hardware interface, that allows intercourse with simulated objects as if they were real (Mandal, 2013). The first known immersive simulator dates back to the decade of the 60's, it was named "Sensorama" and was created by Morton Heilig. Although proper interaction with the environment was still lacking, it provided a surrealistic experience with multisensory impressions (Cipresso, Giglioli, Raya, & Riva, 2018). Another remarkable contribution regarding the concepts of VR was the one made by Sutherland in the same decade, in "*The Ultimate Display*" (Sutherland, 1965) in which he proposed various ways to program a virtual environment with the adequate tools in order to simulate reality to the point in which VR would become indistinguishable from the actual world, and years later, he developed the first "Head Mounted Display" (HMD), with incorporated head tracking that would successfully update whenever there were changes in the user's orientation and position (Mazuryk & Gervautz, 1996), preceding the HMD's that are used nowadays. According to their purpose, two main types of VR have been described: Commercial gaming (CG) systems and purpose-designed Virtual Environments; the latter focusing on the clinical use, with specialized software and hardware, although CG systems may also serve for rehabilitation purposes, with the advantage of having more availability and economic accessibility than purpose-designed VE systems (Lohse, Hilderman, Cheung, Tatla, & Van der Loos, 2014).

VR in psychiatry

An attempt has been made in order to provide better and more efficient therapeutic options or therapeutic coadjutants for pharmacological treatments and cognitive behavioral therapy. VR technology has been explored in order to offer a new approach for the treatment and diagnosis of psychiatric disease, such as anxiety, depressive disorders, drug dependence, post-traumatic stress disorder (PTSD), eating disorders (ED), attention deficit hyperactivity disorder (ADHD), and even schizophrenia.

Substance abuse disorders

Studies have been made in order to validate the efficacy of novel VR programs that may be helpful for the diagnosis and treatment of individuals affected by distinct substance abuse disorders, such as alcohol use disorder (AUD), by inducing craving with specific cues in order to distinguish them from social drinkers (SD) and to develop cue exposure therapies (CET) that can be controlled, individualized, and effective (Ghiță et al., 2019). VR based therapies include traditional cognitive behavioral therapy (CBT) and relapse prevention training with exposure and coping skill practice in virtual environments that are able to induce cue reactivity in order to develop skills that can be applied a-posteriori in real life, and that may also be useful in eating disorders and so, contribute to prevent other conditions such as obesity (Bordnick, Carter, & Traylor, 2011). Analyzes have reaffirmed the benefits for the assessment and management of these disorders, but also highlight the need for proper evaluation of the effectiveness of VR therapies as an exclusive treatment (Segawa et al., 2020).

Anxiety disorders

The main features of anxiety disorders are excessive fear, worry and avoidance that cause significant functional distress in the main activities of the affected individual's everyday life (Katzman et al., 2014). Anxiety and related disorders exist amongst the most commonly found mental disorders, and guidelines have been made for the diagnosis and treatment of panic disorder, agoraphobia, specific phobia, social anxiety disorder (SAD), generalized anxiety disorder (GAD), PTSD and obsessive-compulsive disorder (OCD) (Katzman et al., 2014). According to the emotional processing theory (Foa, Huppert, & Cahill, 2006), fear is a cognitive structure that contains stimuli, responses and meanings, and acts as a program to avoid danger, and in "healthy" individuals, the associations among the representations reflect reality in a faithful way, in contrast to anxiety disorders, in which said representations distort reality and so, excessive response elements are created. Studies have shown the effectiveness of VR based therapies for specific phobias (Landowska, Roberts, Eachus, & Barret, 2018; Suso-Ribera et al., 2019; Wechsler, Kümpers, & Mühlberger, 2019), social phobia (Gebara, Barros-Neto, Gertsenchtein, & Lotufo-Neto, 2016; Gega, White, Clarke, Turner, & Fowler, 2013), agoraphobia (Wechsler et al., 2019), and PTSD (Botella, Serrano, Baños, & García-Palacios, 2015; Maples-keller, Yasinski, Manjin, & Rothbaum, 2017; Rizzo & Shilling, 2017). Studies have shown that VR exposure therapy (VRET) would be more easily accepted by most patients with a specific phobia than traditional (in-vivo) ET, which may suggest an opportunity for the improvement and application of this sort of treatments (Landowska et al., 2018). Meta-analyses have shown that no significative difference exists between in-vivo ET and VRET; while VRET (when properly developed) remains as a more accessible, affordable, and potentially exploitable choice for mental health practitioners and patients (Wechsler et al., 2019). Cognitive Behavioral Therapy (CBT) is another modality of treatment offered to patients who suffer anxiety disorders, and the possibility to use VR technologies has been explored in order to give traditional CBT a more ecological and patient-friendly approach, while keeping the whole benefits and effectiveness of the therapy (Donker et al., 2019).

Depressive disorders

In contrast to anxiety disorders, depression is characterized by episodes of diminished mood, and disinterest, lack of pleasure, difficulty concentrating, and impairment of sleep and dietary habits, which may affect the quality of life of the individual and may eventually lead to suicide (Orsolini et al., 2020). VR exposure and VR-enhanced CBT have been investigated, and their effectiveness has been demonstrated (Fodor et al., 2018). Even if studies regarding therapeutic interventions specifically for depression are vastly outnumbered by those made for other clinical entities, an attempt has been made to explore novel therapeutic approaches for this type of disorders. More research is needed in order to attain a wider vision of VR based techniques for the treatment of depressive disorders.

Eating and weight disorders

Eating and weight disorders (EWD) or eating disorders (ED) are commonly diagnosed in adolescents

and young adults, and more easily found in athletes and females. ED include anorexia nervosa (AN), bulimia nervosa (BN) and binge eating disorder (BED), which are known to cause a wide variety of psychological and medical disturbances and an increased risk of mortality (El Ghoch, Soave, Calugi, & Dalle Grave, 2013). Patients often feel dissatisfied with their bodies and may exhibit other mental disorders, such as depression or anxiety (De Carvalho, Dias, Duchese, Nardi, & Appolinario, 2017). With the aid of VR technology, eating-related anxiety caused by exposure to specific cues, such as virtual food, can be alleviated by modifying dysfunctional thoughts and by doing so, it would increase self-efficacy, disrupting the reconsolidation of adverse food-related memories (Brown et al., 2020). Although VR-assisted CBT has also been investigated for the treatment of these disorders, VR-assisted CET has proven to be more effective in regard to the reduction in overeating episodes and other negative behaviors (Ferrer-Garcia et al., 2019). VR offers great advantages for the assessment and treatment of ED, such as the possibility to visualize actual, perceived and desired body weight or shape of the patient, as well as allowing the clinician to concretely perceive the triggers of binge-eating and evaluate the coping abilities of the patient, while offering the benefits of safety and privacy to the patients, which would make therapy sessions more acceptable for them (De Carvalho et al., 2017). Therapies targeting the negative self-body image perceptions have been proposed for the treatment of EDs and even obesity. One of the aforementioned proposals would be an individually tailored VR event in order to identify the source of the impaired body image by appealing to a spatial cognitive process via a VR-based egocentric-allocentric transformation, and then, attempt to modify the locked image with the help of supervised cognitive therapy focused on body-image rescripting (Riva, 2011). Another proposal is the use of a social virtual world with the aim of increasing self-efficacy in nutrition and exercise among overweight adults by employing VR avatars (virtual representations of the user) that serve as ideal self-models that encourage improvement in healthy habits (Clus, Larsen, Lemey, & Berrouiguet, 2018).

Gender dysphoria

While this term is quite complicated and shrouded in controversy, gender dysphoria (GD) is defined by the DSM-5 as a condition in which a person has a marked incongruence between the expressed or experienced gender and biological sex at birth, which causes distress in important areas of functioning, such as work or in social activities, so the individual often experiences a strong desire to be treated as a person of a different gender (Kaltiala-Heino, Bergman, Työläjärvi, & Frisén, 2018). The care of people with this disorder is multidisciplinary and variable, and may imply cross-sex hormonal treatment or gender reassignment surgery in order to help the dysphoric patient reduce anxiety and stress, and improve overall mental health and quality of life (Costa & Colizzi, 2016). However, treatment poses an ethical and medical challenge, as it is not yet entirely standardized, even if international and in some cases, local guidelines exist (Gerritse et al., 2018). VR-assisted treatment has not yet focused on GD, although some studies have been made in order to achieve a better understanding on self-perception and body-image, and may contribute to develop potential non-invasive VR-assisted treatment options in the future (Feusner et al.,

2016). A study was made in order to assess the effect of gender on the perception of six different hand avatars with the use of VR, and the results yielded that both male and female participants felt discomfort while using hands of the other gender (Schwind et al., 2017). Further research is needed in order to fully understand this phenomenon, and assess the effect that this kind of experiences may have on people with GD.

Schizophrenia

A complex chronic mental health disorder with a wide variety of symptoms ranging from delusions and hallucinations to disorganized speech, sometimes causing disability. Although the etiology of schizophrenia is not entirely understood and is most likely multifactorial, it is theorized that a deficiency or excess of neurotransmitters such as dopamine, serotonin and glutamate is the cause of the development of schizophrenia (Patel, Cherian, Gohil, & Atkinson, 2014). Non-pharmacological treatment options include meta-cognitive training, narrative therapies, mindfulness therapy, cognitive behavioral therapy, personal therapy and compliance therapy; but it is worth mentioning that these therapies work only as a complement for pharmacological treatment, and these therapies have not yet proven effective on their own (Patel et al., 2014). Approaches have been made with the use of VR a psychedelic - assisted therapies in order to reduce symptoms and improve the quality of life of schizophrenic patients, and although research is scarce, progress has been made (du Sert et al., 2018; Park, Kim, Lee, Na, & Jeon, 2019).

VR in other branches of medicine

One of the most studied uses of VR/AR in medicine is the management of pain, either chronic, acute, related to medical procedures and also in pediatric patients (Arane, Behboudi, & Goldman, 2017). Studies have shown significant effectiveness in the reduction of pain when applying VR in different cases, independently of the cause of admission in hospitalized patients and during painful medical procedures such as injections, dressing changing in burned patients, intravenous line replacements and dental interventions (Spiegel et al., 2019). Regarding neurology, VR technologies have proven to be helpful in post-stroke patients. About 30% of patients affected by stroke experience residual disabilities, such as cognitive impairment, often overlooked because of the severe motor disabilities that develop in the same patient (Sun, Tan, Yu, 2014). Studies have shown an improvement on the recovery of cognitive and motor function, especially of upper limbs, when using VR-based rehabilitation programs following a stroke (Aminov, Rogers, Middleton, Caeyenberghs & Wilson, 2018) and some other studies have tested the use of Brain-Computer Interfaces with favorable results, suggesting a promising future for research on these technologies (Cho et al., 2016).

Hallucinogens and psychiatry

Mystical experience reports following the consumption of hallucinogen substances date back thousands of years, and while they represent a very attractive matter of research on their own, this article focused on the therapeutic potential that these substances carry for mental disease. Hallucinogens are

a diverse group of compounds that belong to several different classes according to their pharmacological mechanism of action and chemical structure, but share the common capability to produce deep effects in perception, thoughts and emotions, and may also induce changes in the perception of reality, mystical experiences and in some cases, acute psychosis (Barret & Griffiths, 2018; Nichols, 2016). Commonly investigated substances that fall in this group include the so-called classic hallucinogens (CH): lysergic acid diethylamide (LSD; an ergotamine derived from ergot fungi), psilocybin (a tryptamine found in several genera of mushrooms), mescaline (a phenethylamine found in peyote and other cacti), N,N-dimethyltryptamine (DMT), and 2,5-dimethoxy-4-bromoamphetamine (DOB) (López-Giménez & González-Maeso, 2018; Nichols, 2016; Thomas, Malcolm, & Lastra, 2017). All of the aforementioned share the common characteristic of having a high affinity and agonist at the serotonin 5-HT$_2$ G-protein coupled receptor (GPCR) (López-Giménez & González-Maeso, 2018; Nichols, 2016). Other substances with hallucinogenic properties, although not necessarily labeled hallucinogens include empathogens or entactogens, such as 3,4-methylenedioxymethamphetamine (MDMA), that belongs to a group of mixed serotonin and dopamine reuptake inhibitors and releasers; dissociative anesthetics, which include N-methyl-D-aspartate antagonists, namely ketamine and dextromethorphan; atypical hallucinogens, such as the kappa opioid receptor (KOR) agonist salvinorin A; ibogaine, an indole alkaloid; and anticholinergics such as atropine and datura, known as deliriants (Canal & Murnane, 2017; Garcia-Romeu, Griffiths, & Johnson, 2014; Nichols, 2016). One of the most interesting facts about CH is that they have a very low probability to cause addiction (Canal & Murnande, 2017). Due to the history of structured use (mostly in ritual settings) of hallucinogenic substances since ancient times, some important common aspects that may be of use in a clinical setting should be taken into account, specially restrictions such as the need for guidance, and appreciation for the powerful psychological effects mostly because of their innate ability to produce deep and meaningful spiritual experiences that may become overwhelming for the individual (Nichols, 2016). A large body of evidence suggest their potential use for the acceleration of psychotherapy for the treatment of various psychological disorders, and also highlight that even though some physiological effects may arise (dizziness, weakness, tremors, nausea, drowsiness, paresthesia, blurred vision and increased pulse and systolic and diastolic blood pressure), they remain less impactful for the health of the individual than the psychologic aftermath that they represent for the patient's mental health, even when administered in large doses (Bogenschutz & Johnson, 2016).

Depressive disorders

Psilocybin, a prodrug that is metabolized *in-vivo* to psilocin (4-OH-dimethyltryptamine), has been found to significantly decrease the symptoms of treatment-resistant depression, with effects lasting as long as 3 months, and has also shown effectiveness for the treatment of addiction, cancer-related psychiatric disorders, anxiety and OCD (Carhart-Harris et al., 2017; Griffiths et al., 2016; Johnson & Griffiths, 2017). Psilocybin is known to moderately increase blood pressure, and due to its intense psychological effects,

candidates for structured psychotherapy must be carefully selected, and prepared in order to undertake the sessions properly and with the less adverse effects as possible. Candidates must exclude those patients at risk for the development of psychotic disorders, and patients with cardiovascular risk mainly; although monitoring is still risky due to the dangerous reactions that may be caused by the intense psychological experiences that the use of psilocybin carries (Johnson & Griffiths, 2017). Among the psychological properties of psilocybin, studies have found the potential of producing deep and lasting changes in personality traits, such as political views and nature relatedness, as was demonstrated in the work by Lyons & Carhart-Harris (2018). A review made by Heuschkel and Kuypers (2020) concluded that the combination of mindfulness meditation along with psilocybin may serve as a useful tool for psychedelic therapists. Ayahuasca is a traditional Amazonian religious-ritual decoction, and is made from the bark of *Banisteriopsis caapi*, which is a vine rich in beta-carboline harmala alkaloids such as harmaline and harmine (monoamine oxidase inhibitors or MAO), usually in combination with the leaves of *Psychotria viridis* bushes, rich in DMT, which without these substances would otherwise be inactivated by the gut and liver MAOs. This ancient combination of ingredients has been empirically understood and employed by Amazonian populations to heal various psychological or psychosomatic illness, including anxiety and depression. Psilocybin has been found to have a lower rate of adverse reactions compared to ayahuasca, which frequently cause nausea and vomiting (Palhano-Fontes et al., 2019). Past investigations have shown therapeutic potential for depressive disorders with the use of LSD, although it has proven more suitable for the treatment of other disorders, especially addiction (Fuentes, Fonseca, Elices, Farré, & Torrens, 2020). Ketamine has also been studied because of the rapid antidepressant properties that it exhibits (Krediet et al., 2020).

Substance abuse disorders

Mystical experiences caused by psilocybin have been found to develop deep and persisting psychological effects in individuals that consume it, most of the times improving behavior, attitude and values, among others. Psychedelics have been tested as an alternative therapy for addiction, with promising results. Studies with LSD for heroin use disorder showed significant differences in total abstinence rates, and other studies have shown effectiveness improving the quality of life of alcoholic subjects when using LSD for alcohol abuse disorder, although data on alcohol abstinence was unclear (Fuentes et al., 2020). Ibogaine, a natural alkaloid obtained from the bark of the African *Tabernanthe iboga*, has been studied as a therapeutic agent for the detoxification of individuals with chronic opioid use, and has proven effectivity by reducing withdrawal symptoms significantly, confirming findings in research made decades ago (Davis, Barsuglia, Windham-Herman, Lynch, & Polanco, 2017).

Anxious disorders

Evidence suggests that psilocybin is effective in reducing anxious symptoms in patients with cancer (Daniel & Haberman, 2017; Johnson & Griffiths, 2017), as well as in patients with life-threatening diseases, and also exhibited significant reductions in the symptoms

of people with OCD (Baumeister, Barnes, Giaroli, & Tracy, 2014; Daniel & Haberman, 2017).

Information about the use of other classical hallucinogens for the treatment of anxious disorders is still required, but past research has shown effectiveness of psychotherapy in conjunction with LSD for the treatment of anxiety-related disorders (Fuentes et al., 2020). Studies have also pointed out a potential of use of MDMA assisted psychotherapy as a minimal risk therapeutic method that works by reducing fear response to traumatic memories, while enhancing introspection and increasing interpersonal trust, which improves the patient-therapist relationship and so, the effectiveness of the therapy (Krediet et al., 2020). Other substances such as LSD or psilocybin might also be effective, although the inherent psychoactive intensity of these compounds might make them less ideal than MDMA. Ketamine has also been considered for the treatment of PTSD, although information on this matter is still lacking (Krediet et al., 2020; Reiff et al., 2020).

Eating disorders

Information on the use of psychedelics and psychedelic assisted therapies for the treatment of eating disorders is insufficient, but investigation with psilocybin on animal models (Foldi, Liknaitzky, Williams, & Oldfield, 2020) has suggested a possible positive impact for this substance in the future of eating disorders.

Gender dysphoria

Up to the date, no formal research on psychedelics has been made in people with gender dysphoria, and information on this topic is scarce, but it has been proposed that psychedelic assisted therapy, may improve the patients' health outcomes by decreasing identity threat by increasing access to gender affirmation with the help of a therapist and reducing the need for gender affirmation from others. MDMA has been suggested for this kind of therapy, as it is known to increase self-compassion and self-love, which is desirable and needed in order to reconnect dysphoric individuals with oneself and others (Sevelius, 2019).

Material and methods

A systematic literature review using the PRISMA methods (Moher et al., 2015) was conducted using the databases: PubMed, Medline, Embase, Cochrane Library, Scopus and Web of Science, with the input of various combinations of the following key words: "Psychedelic", "Hallucinogen", "Virtual Reality", "VR", "Psychiatric disorders", "Addiction", "Gender Dysphoria", "Schizophrenia", "Depression", "Obsessive Compulsive Disorder", "Psychiatry", "Anxiety", "Post traumatic stress disorder", "Eating disorders" "PTSD". Some other studies were obtained through screening references from relevant articles.

Peer-reviewed articles regarding the use of psychedelics and/or VR for the treatment of psychiatric disorders were included with the following criteria: 1) These were written in English, 2) the success of the therapy is objectively measured, 3) the studies must be clinical trial articles or case studies, and 4) the reference titles must have mentioned virtual reality or VR and / or psychedelics / hallucinogens along with the terms related to psychiatric disorders. Qualitative studies,

protocols for studies or studies that were not related to psychiatric pathology were excluded. Studies with the use of substances with hallucinogenic properties, although not necessarily labeled as hallucinogens such as ketamine and MDMA were included in this review.

Results

Using the process described in the PRISMA flowchart (Figure 1), a total of 130 documents were identified through the search in PubMed, Cochrane, Medline, Scopus Embase and Web of Science, and 18 additional records were found through other sources (manual search and meta-analysis). After removing duplicates and excluding manuscripts based on titles or abstracts, 68 manuscripts were screened in more detail in order to verify eligibility. Subsequently, other 45 manuscripts were excluded, resulting in the 23 manuscripts used in this systematic review. The most relevant findings (year, sample, method, measurement and results) are summarized in **tables 1** and **2**. In general, the results yielded in all of the studies reflected improvement of the symptoms, although some of them lasted longer than others, and some acted faster than others.

Use of VR

Of the 23 studies assessed in this review, 11 of them addressed the use of VR-assisted therapies: four of them covered specific phobias (social phobia, arachnophobia, and kinesiophobia), two studies focused on eating disorders, other two of them focused on PTSD, another one of them addressed gambling disorders, one also focused on preoperative anxiety and the last one targeted schizophrenia. The main characteristics of the studies addressing the use of VR are summarized in **table 1**.

VR for phobia

In the three-arm randomized controlled trial by Bouchard et al. (2017a), VR exposure in CBT for the treatment of Social Anxiety Disorder was investigated in order to demonstrate it is more practical and effective than in-vivo exposure. A final sample of 59 adults between 18 and 65 years with a primary DSM-5 diagnosis of Social Anxiety Disorders were randomly assigned to either VR exposure (n=17), in vivo exposure (n=22) or waiting list (n=20), and were assessed with the use self-administered instruments, such as the Liebowitz Social Anxiety Scale-Self Reported Version (LSAS-SR), Social Phobia Scale (SPS), Social Interaction Anxiety Scale (SIAS), and Fear of Negative Evaluation (FNE), defining statistically significative change as a change index on either the LSAS-SR or FNE. Patients in the *in virtuo* exposure group were exposed to 8 scenarios with the help of an HMD, and a motion tracker. The scenarios used in this study were a speech in front of an audience in a meeting room, having a job interview, introducing oneself and having a talk with relatives in an apartment, acting under the scrutiny of strangers on a coffee shop patio, and facing criticism or insistence in 2 situations, and a neutral scenario without characters used to familiarize patients with VR. The results showed a reliable change from pre to post-treatment in 76.5% of participants who received CBT and VR exposure in contrast to the participants that received CBT with *in vivo* exposure (68.3%), and the waiting-

Table 1. *Results of Studies with VR*

Study	Population	Procedure	Most relevant measurement	Outcome
Bouchard et al. (2017a)	n= 59 Adults with social anxiety disorder	VRET	LSAS-SR, SPS, SIAS, FNE	Improvement on all outcome measures, maintained at 6 month-follow-up
Gebara et al. (2016)	n= 21 Patients with social phobia	VRET	LSAS, CGI, SF-36, SUDs, BDI, SAS, ATQ 30, DAS	General improvement, decreases in fear, anxiety and avoidance of social situations
Fowler et al. (2019)	n= 16 Veterans with kinesiophobia	VR distraction-to-exposure hierarchy	POC-VA, FDAQ, Pain Catastrophizing Scale	Improvements observed in interference with mobility and pain intensity
Miloff et al. (2019)	n= 100 Phobic patients	VRET	Behavioral approach test	Non-inferiority against gold standard was identified
Marco et al. (2013)	n= 34 Female patients with EDs	CBT + VR	BAT, BIATQ, BASS, SIBID, BITE, EAT	Improvement in all body image and psychopathological measures
Ferrer-Garcia, et al. (2019)	n= 58 Patients with EDs	VR assisted CET	Body Dissatisfaction, Drive for thinness, ED inventory-3, STAI, FCQ-T, FCQ-S	Overall improvement. Significative lower symptoms after 6 months follow-up
Beidel et al. (2019)	n= 92 Patients with PTSD	VRET + psychoeducation	CAPS, PCL-M, M-FAST, CGI, HAMD, HAMA, Self-Monitoring	Significant reduction in PTSD symptoms
Norr et al. (2018)	n= 162 Active duty U.S. army soldiers with PTSD	VRET + Prolonged Exposition (PE)	BDI-II, CAPS	Reduction in suicidal ideation and PTSD symptomatology
Dehghan et al. (2019)	n= 40 children with pre-operative anxiety	VRET	Yale preoperative Anxiety Scale questionnaire	Children in interventional group expressed lower anxiety in comparison with control group
Bouchard et al. (2017b)	Study 1: n= 28 Study 2: n= 34 Study 3: n= 25 Pathological gamblers	VR + CBT	LSAS-SR, SPS, SIAS, FNE, BDI-II	Significative reduction in craving and desire for gambling, but not superior to control treatment
du Sert et al. (2018)	n= 19 Patients with Schizophrenia or Schizoaffective disorder	VR- assisted therapy	PSRATS, BAVQ-R, PANSS, BDI-II, Quality of life Enjoyment and Satisfaction Questionnaire-Short Form	Reduction of AVH symptoms and related distress. Reduction of general and depressive symptoms. Improvement in quality of life

36-item short-form Health survey (SF-36), Auditory verbal hallucinations (AVH), Automatic thoughts Questionnaire (ATQ 30), Beck Depression Inventory (BDI), Beck Depression Inventory-II (BDI-II), Beliefs about voices questionnaire-revised (BAVQ-R), Body Areas Satisfaction Scale (BASS), Body Attitude Test (BAT), Body Image Automatic Thoughts Questionnaire (BIATQ), Bulimic Investigatory Test Edimburgh (BITE), Clinical Global Impressions Scale (CGI), Clinician-Administered PTSD Scale (CAPS), Cognitive Behavioral Therapy (CBT), Cue Exposure therapies (CET), Death Anxiety Scale (DAS), Eating Attitudes Test (EAT), Fear of Daily Activities Questionnaire (FDAQ), Fear of Negative Evaluation (FNE), Food craving Questionnaire trait (FCQ-T) and state (FCQ-S), Hamilton Rating Scale for Anxiety (HAMA), Hamilton Rating Scale for Depression (HAMD), Lievowitz Social Anxiety Scale Self-Administered Version (LSAS-SR), Miller Forensic Assessment of Symptoms (M-FAST), Pain Outcomes Questionnaire-VA (POC-VA), Positive and negative Syndrome Scale (PANSS), Post-Traumatic Stress Disorder (PTSD), Psychotic symptoms rating scale (PSRATS), PTSD Checklist – Military Version (PCL-M), Situational Inventory of Body Image Dysphoria (SIBID), Social Interaction Anxiety Scale (SIAS), Social Phobia Scale (SPS), Spielberger Self-rating State-trait Anxiety Scale (SAS), Subjective Units of Discomfort (SUDs), and VR exposure therapy (VRET).

list (30%), thus, demonstrating that VR-assisted CBT is an effective, efficient and more practical alternative to classical CBT.

In the open clinical trial made by Gebara et al. in 2016, the therapeutic potential of VR as a treatment for social phobia was examined. A final sample of 21 subjects between 18 and 65 years old, meeting the DSM-IV criteria for social phobia were evaluated with the use of The Research Version of the Social Phobia Structured Clinical Interview for DSM-IV-TR Axis I disorders, Patient Edition, the Liebowitz Social Anxiety Scale (LSAS), the Clinical Global Impression Scale (CGI), The Medical Outcome Studies 36-Iten Short-Form Health Survey (SF-36), translated in Portuguese, validated for use in Brazil, Subjective Units of Discomfort, Scale for Measuring Therapy Sessions

Table 2. *Results of Studies with Hallucinogenic Substances*

Study	Population	Procedure	Most relevant measurement	Outcome
George et al. (2017)	n=16 Treatment resistant depression	Subcutaneous ketamine	MADRS	Improvement in depressive symptoms
Lapidus et al. (2014)	n= 20 Treatment-resistant depression	Intranasal ketamine	MADRS	Significant improvement in depressive symptoms within 24 hours
Bretas Bastos et al. (2012)	n= 80 Depressive patients selected for surgery	Epidural ketamine	HAMD	Improvement in the severity of depression
Sos et al. (2013)	n= 27 Depressive patients	Ketamine	MADRS	Induction of antidepressant effect
Krupitsky et al. (2002)	n=17 Detoxified heroin-addicted patients	Ketamine + psychotherapy	SIDI, ZDS, SAS, VASC, SA, HRS, MMPI, LCS, CTA, PLT, Spirituality Changes Scale	Significant reduction in craving, in components of anhedonia and state and trait anxiety. Significant increase in self-sufficiency.
Bogenschutz et al. (2015)	n= 10 Patients with alcohol dependence	Psilocybin + psychotherapy	POMS, AASE, PACS	Positive changes in mood and craving, improvement in self-efficacy
Carhart-Harris et al. (2017)	n=19 Patients with treatment resistant depression	Psilocybin	QIDS-16	Rapid and sustained antidepressant effects
Carhart-Harris et al. (2018)	n=20 Patients with severe unipolar major depression	Psilocybin	QIDS-16	Sustained antidepressant effects after 6 months
Griffiths et al. (2016)	n= 51 Anxious/ depressive patients with cancer	Psilocybin	STAI-T, HAMA, BDI, HAMD	Substantial and enduring decreases in anxiety and depression
Agin-Liebes et al. (2020)	n= 15 Patients with cancer and anxiety/depression	Psilocybin - assisted therapy	HADS, HADS-D, HADS-A, STAI, STAI-S, STAIT-T, DAS, HAI, DS, WHOQOL-BREF, FACIT-Sp-12, Persisting effects questionnaire	Large and lasting reductions in anxiety, depression, hopelessness, demoralization and death anxiety
Palhano-Fontes et al. (2019)	n= 29 Patients with treatment-resistant major depressive disorder	Ayahuasca	MADRS, HAMD	Rapid antidepressant effect, significant improvements in psychiatric scales
Mithoefer et al. (2018)	n=26 Patients with chronic PTSD	MDMA -assisted psychotherapy	CAPS-IV	Significant reductions in PTSD symptoms

Alcohol Abstinence Self-Efficacy Scale (AASE), Beck Depression Inventory (BDI), Clinician-Administered PTSD Scale IV (CAPS-IV), Color Test of Attitudes (CTA), Demoralization Scale (DS), Dysfunctional Attitude Scale (DAS), Functional Assesment of Chronic Illness Therapy-Spiritual Well-Being (FACIT-Sp-12), Hallucinogenic Rating Scale (HRS), Hamilton Rating Scale for Anxiety (HAMA), Hamilton Rating Scale for Depression (HAMD), Hopelessness Assessment in Illness (HAI), Hospital depression and anxiety scale (HADS) for Anxiety (HADS-A) and Depression (HADS-D), Locus of Control Scale (LCS), Minnesota Multiphasic Personality Inventory (MMPI), Montgomery Asberg Depression rating scale (MADRS), Penn Alcohol Craving Scale (PACS), Post-Traumatic Stress Disorder (PTSD), Profile of Mood States (POMS), Purpose-in-Life-Test (PLT), Quick Inventory of Depressive Symptomatology-Self Report (QIDS-SR16), Scale of Anhedonia Syndrome (SA), Spielberger Self-rating State-trait Anxiety Scale (SAS), State trait anxiety inventory (STAI) for state (STAI-S) and anxiety (STAIT-T), Structured clinical Interview for Psychiatric Disorders (SIDI), Visual Analog Scale of Craving (VASC), World Health Organization Quality of Life-Brief Version (WHOQOL-BREF), and Zung Self-rating Depression Scale (ZDS).

(created for this study) that allows participants to assess how much virtual scene resembles real situations. Also, The Beck Depression Inventory (BDI), the Sheehan Disability Scale (SDS), the Social Adjustment Scale (SAS), the Automatic Thoughts Questionnaire (ATQ-30), and a Brazilian adaptation of the Dysfunctional Attitude Scale (DAS) were used. Two Virtual 3D scenarios of anxiety-generating social situations were created specifically for this study, merging motion capture of real actors with interactive characters. One

of the scenarios was about walking down on the street, approaching people, and the other one was at a party, welcoming guests, engaging in conversation and taking and giving speech. The hardware used was a PC with Windows 7 operating system, polarized passive 3D glasses, a micro-polarized LCD screen with resolution of at least 1,366 x 768 pixels or a 3D TV or monitor, ear headphones for sound immersion, and a keyboard for interaction with the program. The results showed an average reduction in anxiety of 72.5% after exposure to the scenes, and the average number of sessions needed to complete treatment was 7, and the duration of exposure until habituation was 21.29 minutes, hence, the objective of the study was successful, but it is worth mentioning the fact that they did not use a HMD, which may have had a positive impact in the level of immersion.

A hybrid type 1 implementation-effectiveness study made by Fowler et al. (2019) examined the feasibility of VR as an adjunctive intervention for veterans with kinesiophobia due to chronic pain. The final sample consisted of 16 veterans with diagnosis of chronic pain syndrome and a negative screen for illicit substances, excluding those with uncontrolled medical and psychological factors that could interfere with the rehabilitation program in which they were enrolled. A distraction-to-exposure intervention was conducted, starting with low stimulation intensity, and moving to high movement intensity. Veterans alternated between oculus rift and Samsung Oculus Gear VR. 12 commercially available VR apps, six per HMD were chosen to fit the levels of intensity, low-intensity distraction apps included mindfulness meditation and visual imagery, as only minimal movement is required. The medium intensity apps include virtual walking or swimming, controlling an aircraft or watercraft, requiring neck movement. High intensity apps included 3D painting, and music or rhythmic-based apps, which require upper extremity and torso movement. Kinesiophobia was assessed with the use of the Pain Outcomes Questionnaire-VA (POQ-VA), and Fear of Daily Activities Questionnaire (FDAQ). Veterans completed 20 minutes of VR during daily physical therapy sessions, and each session, they were asked which intensity VR apps they would like to use during that session. Some limitations emerged, principally concerning technical difficulties during the study, such as inconsistent wi-fi source, the lack of a kiosk mode, and a need to restart the apps during sessions, as well as other factors such as environmental noise, situations that may have hindered immersion. In regard of the results, the Minimum Clinically Important Difference (MCID) for kinesiophobia indicated that 38% exceeded MCID on the FDAQ, and after the removal of an outlier, a small effect size improvement was noted for the primary outcome fear of movement when using the FDAQ, but not the POQ-VA.

The parallel-group randomized non-inferiority trial carried out in Sweden by Miloff et al. (2019) compared the efficacy of a single session of technician-assisted virtual reality exposure therapy for the treatment of spider phobia. A final sample of 100 participants with spider phobia were randomized to OST or VRET, measuring in-vivo spider avoidance with the help of a BAT, which was completed pre-assessment, post-assessment and at a 3- and 12-month follow-up. Other measures were used, such as The Structured Clinical Interview for DSM-IV Axis-I Disorders (SCID-I/P), Spider Phobia Questionnaire (SPQ), Generalized Anxiety Disorder Assessment (GAD-7), Patient Health Questionnaire (PHQ-9), The Brunnsviken Brief Quality of Life

Inventory (BBQ), The Negative Effects Questionnaire (NEQ-32, the Igroup Presence Questionnaire (IPQ). The hardware used was a Samsung Gear VR system, which comprised 2 Samsung smartphones and the VR Headset, which includes a touchpad, back button, volume buttons, and a focus adjustment wheel, and the VRET application was called VIMSE, and consisted in 8 levels of increasingly realistic spiders, in which the participants had full control over how quickly they progressed through them with the support of a virtual therapist and spider expert who provided feedback. The results showed strong reductions in spider phobia symptoms and behavioral avoidance in both groups, and non-inferiority was identified after 3 months, as was expected. not all participants were able to complete the primary outcome measure, VR tools such as VIMSE are still in an early stage of development, and the skills of the therapists were not systematically evaluated prior to the intervention. Nonetheless, the conclusion was that even if in-vivo exposure therapy remains as the gold standard for phobia management, the benefits of VRET are not worse over follow-up.

VR for eating disorders

The controlled study made by Marco, Perpiñá, C., & Botella (2013) aimed to compare the benefits between the use of CBT alone versus CBT with VR for the treatment of EDs. The sample was obtained from an outpatient program for EDs, in a hospital in Castellón, Spain. Participants had been diagnosed with ED with the use of SCID-I and SCID-II in accordance with DSM-IV-TR. Patients with a Body Mass Index (BMI) <16, with substance abuse, high suicide risk and/or serious personality disorders were excluded. The final sample comprised 34 female patients between 15 and 40 years old, with an average age of 21.82 and a BMI ranging from 16 to 32 with an average of 21.5, of which 17 were diagnosed with Bulimia Nervosa, 12 with Eating Disorder not otherwise Specified (EDNOS) and 5 patients were diagnosed with Anorexia Nervosa. The length of time with EDs was 1 to 16 years, with an average of 4.17. Body Attitude Test (BAT), Body Image Automatic Thoughts Questionnaire (BIATQ), Body Areas Satisfaction Scale (BASS), Situational Inventory of Body-Image Dysphoria (SIBID), The Bulimic Investigatory Test, Edinburgh (BITE), the Eating Attitudes Test (EAT) and a weekly evaluation of symptoms specially designed for this research were all employed in order to assess the multiple different dimensions of the primary outcome measure of this research, which was Body- Image. Regarding the treatment, 2 components were determined: the first was CBT for either BN or AN, and the other was CBT for body image in eating disorders using VR organized in 15 CBT group sessions and 8 individual psychotherapy sessions with VR techniques in 3 stages: Stage 1 comprised 3 sessions in which the participants had to become aware of their body image issues, Stage 2 comprised sessions 4 through 13, and the objective was to change beliefs and attitudes about body and appearance, and stage 3, comprising sessions 14 and 15, with the objective of consolidating the achievements of the previous stages. 5 virtual environments denominated "areas" were used in stages 1 and 2, and consisted in various interactive exercises in order to assess body image and weight, and to show the patients the discrepancies between their real bodies and their perceived body image. The technological apparatus that was used consisted in an application developed on World Up software with

sense8. The hardware consists of a desktop penntium III PC, accelGraphics AccelEclipse graphic card and a HMD type V6 by Virtual Research with a 2D mouse. The measurements were evaluated at 3 points: pre-treatment, post-treatment and a 1-year follow-up. The final sample consisted of 18 participants, and demonstrate that all participants improved their body image in a statistically significative way after the one year follow-up, and patients that received VR-assisted CBT showed greater improvement compared to the only-CBT group, and showed more post-treatment improvement, which continued to rise at the one year follow-up in terms of the measured Body Attitudes Test (BAT), Body Image Automatic Thoughts Questionnaire (BIATQ), Body Areas Satisfaction Scale (BASS) and Situational Inventory of Body Image Dysphoria (SIBID).

Another study addressing eating disorders was conducted by Ferrer-Garcia et al. (2019). This randomized, multicenter, parallel-group study was conducted at 5 clinical sites in 3 European cities, and aimed to compare virtual reality cue-exposure therapy against additional cognitive behavioral therapy (A-CBT). The initial sample consisted of 35 patients with BN and 29 with BED, with active episodes of binge eating during the last 2 weeks of a structured program of CBT, excluding those with comorbid severe mental disorders. 27 participants were randomized to the A-CBT group and 31 patients were assigned to the VR-CET group. Patients were assessed in the pre-randomization phase, at the end of second-level treatments and after 6 months. Only 58 patients completed the 6-month follow-up assessment. The hardware used for this study was a 6.5-inch 3D laptop with polarized glasses, a computer mouse and earphones, and the software consisted of 4 virtual settings: a bakery-café, bedroom, dining room and kitchen, as well as 2D images of 30 different foods, to which users are exposed in order to measure the craving with the use of a visual analogue scale (0-100). The measures in the study were assessed with the use of: Eating Disorders Examination Interview, and subscales, EDI-B, EDI-BD, EDI-DT, FCQ-T, FCQ-S, State Trait Anxiety Inventory for Trait (STAI-T) and state (STAI-S), and similarly to the previous study, the results demonstrated a significant reduction in symptomatology that was maintained at the 6 month-follow-up. A reduction in overeating episodes, purging episodes, food craving and anxiety was demonstrated and was lower in patients who engaged in the VR-CET group, with large or very large effect sizes of this differences.

Post traumatic stress disorder

The randomized controlled trial made by Beidel et al. (2019) examined the utility of VRET for the treatment of combat related PTSD and examined how the group treatment of trauma management therapy specifically enhances treatment outcome for depression, anger, and social isolation in comparison to a psychoeducation control group. The final sample comprised 92 veterans who had experienced a combat-related traumatic event during military service in Operation Enduring Freedom, Operation Iraqi Freedom, Operation New Dawn, and believe they were suffering from PTSD. Forty-nine patients were randomized to trauma management therapy (TMT) and 43 were randomized to Exposure Therapy, which unlike prolonged exposure therapy, exposure continues until sessions habituation is achieved, based on self-reported

distress. Participants were assessed with the use of the Clinician-Administered PTSD Scale (CAPS), PTSD Checklist – Military Version (PCL-M), Structured clinical interview for DSM-IV (SCID I and SCID II), Miller-Forensic Assessment of Symptoms Test (M-FAST), Clinical Global Impressions Scale (CGI), Hamilton Rating Scale for Depression (HAM-D), Hamilton Rating Scale for Anxiety (HAM-A), and self-monitoring. The results demonstrated a statistically significant improvement of symptoms, decreasing by an average of 41.7 points the CAPS, and with 42-to 50% of each group with significant changes maintaining the benefits for as long as six months demonstrating the effectivity of VRET as an intervention for combat-related PTSD. One important limitation of this study is that it did not compare the intensive exposure method used to a different exposure model, and the treatment was long and extensive, with many components (Sessions of group treatment and psychoeducation, 29 in total, counting VRET) that may mask the effectivity of VRET.

The randomized clinical trial made by Norr, Smolenski & Reger (2018) sought to investigate the effects of exposure therapy on suicidal ideation among active duty military personnel with PTSD, comparing Prolonged Exposure (PE) to VRET and a wait-list control group in the treatment of PTSD stemming from deployments to Iraq of Afghanistan. A final sample of 162 active-duty U.S. army soldiers with the DSM-IV-TR diagnosis of PTSD were included. It is worth mentioning that participants in this study used psychiatric medication such as antidepressants and benzodiazepines. Assessments were conducted at baseline, mid-treatment and post-treatment, with the use of BDI-II, CAPS, and registering whether Suicidal Ideation was present or not. The results showed positive results in regard of symptoms and of suicidal ideation, a statistically significative reduction was observed in the patients treated with PE and VR in comparison with the waitlist control, but it should be noted that this study did not compare the measurements between the group treated with VR exposure and the group that received only prolonged exposure. It must also be noted that it was not possible to determine the temporality of the reductions in symptomatology.

Preoperative anxiety

The Solomon four-group interventional study in a randomized controlled trial design made by Dehghan, Jalali & Bashiri (2019) investigated the effect of VR technology on pre-operative anxiety in children. A final sample of 40 children, 31 boys and 9 girls booked for abdominal surgery between the age of 6 and 12 years old, and without previous history of abdominal interventions. The patients were placed in front of a computer monitor and were presented the simulated steps of going to an operation room, and headphones were used in order to obtain a greater feeling of immersion, and the parents of the patients were requested to touch and caress the children prior to operation. The instrument of measurement was the standardized Yale Preoperative Anxiety Scale questionnaire, and the results showed that children in the interventional groups with pretest-posttests and control groups with posttest had a significant reduction in the preoperative anxiety score after therapeutic exposure using VRET, while no significative change was found in the control group.

Gambling disorders

The only paper in this review addressing gambling disorders was the one written by Bouchard et al. (2017b) in which 3 studies in order to describe different aspects of this disorder and the use of VR. The first study describes whether virtual environments developed specially for gambling disorders can induce an urge to gamble. 28 frequent players (once a month) between 18 and 65 years old and 36 occasional players (twice a year) were recruited, and the infrequent gamblers served as a control group. Participants were invited to play in each of the following games for 7 minutes: Scrabble; a real video lottery terminal (VLT) game in which they gambled $20; in a virtual bar with VLTs; and in a virtual casino. After each game, the Gambling Craving Scale (GCS) was administered after each game, with subscales examined separately. The results demonstrated that frequent gamblers gambling on a real VLT or in VR show a significantly higher anticipation and desire to gamble, in contrast with infrequent gamblers. Study 2 addressed the clinical usefulness of a treatment protocol comprising 2 VR immersion sessions. 34 participants with DSM-IV-TR diagnosis of pathological gambling were randomly assigned to either traditional 28-day CBT with 2 imaginal exposure exercises, and 20 of them received the same treatment regime, but instead of receiving imaginal exposure, they received 2 VR exposure exercises. The apparatus consisted of a Vuzix iWear VR920 and a CUBE motion tracker, and gamblers were asked to imagine gambling situations that trigger cravings and relieve these experiences for about 20 minutes. Patients completed the GCS, and evaluated their desire to gamble in a scale from 0 to 10. Results revealed a significant reduction in craving in participants who underwent VR immersion, but also in participants who underwent imaginal exposure, with no significant difference between groups, but therapists report to be more satisfied with the use of VR, as it was found to be more helpful to determine relevant information about the patients' thoughts, behaviors, and high-risk situations. The third study evaluated the safety of a four-session treatment program of CBT in VR. 25 adults with DSM-5 criteria for gambling disorders were randomly assigned to either VR stimuli condition (n=11) or control imaginal stimuli (n=14), and received either only VR immersion or Imaginal immersion in accordance to each group, but received 4 CBT sessions dedicated to immersion in this study. An in-house questionnaire was administered immediately after the session in order to assess the safety of VR induced cravings, and the results demonstrated that VR does not induce an urge to gamble that persists post-session longer or more strongly than after imaginal therapy.

Schizophrenia

The 7-week phase-II randomized, partial cross-over trial by du Sert et al. (2018) sought to investigate the therapeutic effects of VR for schizophrenic patients, namely on those affected by auditory verbal hallucinations. Nineteen schizophrenic or schizoaffective patients with an age of 18 or more years old who had been hearing persecutory voices and did not respond to at least two antipsychotics were recruited and were randomly allocated to either VRET or received treatment-as-usual (TAU). The VRET in this case consisted in seven weekly sessions, and in the first one, with the Unity 3D game engine,

and Morph 3D Character System, patients created an avatar best resembling the most distressing person or entity believed to be the source of the voice, specifically designed to closely have the face and voice of the "persecutor". The voice of the persecutor was simulated in real-time with a voice transformer Roland AIRA VT-3. The hardware consisted of a Samsung Galaxy S6 smartphone and a Samsung GearVR HMD, and the virtual environment comprised the avatar standing in the dark from a first-person perspective, and the therapist induced a dialogue with the avatar to improve emotional regulation and assertiveness, in order for the patient to become progressively empowered and assertive. Auditory verbal hallucinations (AVH), as well as related beliefs of omnipotence and malevolence were assessed with the Psychotic Symptoms Rating Scale (PSYRATS) and Beliefs About Voices Questionnaire-Revised (BAVQ-R), and psychiatric symptoms were assessed with the Positive and Negative Syndrome Scale (PANSS), BDI-II and quality of life was also evaluated with the Quality of Life Enjoyment and Satisfaction Questionnaire-Short Form. The results reported significant improvements in the severity of AVH, as well as in the beliefs about voices, while psychiatric symptoms diminished and quality of life also improved.

Use of psychedelics

About this topic, 12 of the papers in this review contemplated the use of psychedelics and psychedelic assisted therapies: five of them covered the use of ketamine for different disorders, five of them focused on the treatment of anxiety and/or depression or alcohol abuse with psilocybin, one of them addressed the use of ayahuasca for mayor depressive disorder, and the last one of the studies concerned the treatment of PTSD in veterans with the use of MDMA. The main characteristics of the studies addressing the use of hallucinogens and MDMA can be seen in **table 2**.

Ketamine

The study by George et al. (2017), a double blind, controlled, multiple-crossover study with 6-month follow up, aimed to assess the efficacy and safety of subcutaneous ketamine as a novel therapeutic method for treatment-resistant depression in geriatric patients. Sixteen patients with an age of 60 years or older, with a DSM-IV diagnosis of major depressive disorder or bipolar disorder with a depressive episode longer or equal to 4 weeks, with a Montgomery-Åsberg Depression rating Scale (MADRS) score ≥ 20 and insufficient therapeutic response to ≥ adequate trial of an antidepressant medication during the current episode (defined by Antidepressant Treatment Response Questionnaire) were included. Patients received subcutaneous doses of ketamine HCL in an ascending dose, starting with 0.1 mg/kg and ending with 0.5 mg/kg (according to response) in separate sessions at least a week apart. Midazolam (0.01mg/kg) was randomly inserted in the first 3 treatment sessions, serving as an active control to optimize study blinding. The primary outcome measure was MADRS, assessed by blinded raters, and also hemodynamic and psychotomimetic outcomes were measured. The results reported acute response and remission rates of 68.8% in 11 of 16 participants, concluding that in general, subcutaneously administered ketamine in older patients was effective, safe and well tolerated, causing discrete increases in

heart rate and blood pressure, and occasional reports of mild neurological symptoms.

Another placebo-controlled study with crossover design with the use of ketamine was conducted by Lapidus et al. (2014), but in this case, it was administered intranasally, in order to facilitate therapeutic delivery. Twenty patients with treatment-resistant depression currently in a major depressive episode were randomized to receive 50 mg of intranasal ketamine hydrochloride, or 0.9% saline solution with one of two treatment orders: ketamine – placebo or placebo – ketamine with 1-2 weeks between treatments. Eighteen patients received both treatments under randomized, double-blind conditions. Significant improvement in depressive symptoms were observed within 24 hours after ketamine administration compared to placebo, being well tolerated, with almost no psychotomimetic or dissociative side effects or visible hemodynamic changes, demonstrating the rapid antidepressant effect of intranasally administered ketamine.

A study made by Bretas Bastos, Pereira, & Pereira (2012) investigated the effect of intraoperative sedation of S-ketamine on depression. Eighty patients from 60 to 83 years old, selected for surgery under epidural anesthesia were classified as depressed or non-depressed, and were randomized into 2 sub-groups, D1, D2, ND1 and ND2. Sub-groups D1 and ND1 received S-ketamine and midazolam, while groups D2 and ND-2 only received midazolam. Depression was assessed with the use of the Hamilton Depression Rating (HDR), applied pre-operatively and post-operatively. Results demonstrated a decrease of the mean HDR score from the preoperative value on the second postoperative day in the S-ketamine plus midazolam group. No relevant side effects were reported.

The double-blind, cross-over, randomized, placebo-controlled study by Sos et al. (2013) aimed to demonstrate that changes in prefrontal theta cordance 24 hours after a single infusion of ketamine (0.54 mg/kg) would predict a sustained antidepressant response. A group of 27 hospitalized depressive patients on stable antidepressant medication was assessed and antidepressant response was defined as a 50% decrease of depressive symptoms evaluated 4 and 7 days after the infusion. Three electroencephalographic segments obtained before, after the infusion and 24 hours after dosing were entered into spectral analyses. Eleven responders to ketamine in comparison to 16 non-responders showed significant difference in cordance values at the end of ketamine infusion, which correlated positively with a decrease in MADRS scores on the fourth day after infusion.

Although most of the studies reviewed in this article regarding ketamine address depression in different settings, the double-blind clinical trial made by Krupitsky et al. (2002) investigated the effects of ketamine-assisted psychotherapy on heroin addiction. Seventy detoxified heroin-addicted patients aged between 17 and 26 were randomly assigned to 1 of 2 groups, a group of 35 subjects received existentially oriented psychotherapy plus a psychedelic dose of intramuscular ketamine (2 mg/kg), and another group of 35 subjects received the same kind of therapy, but with a 0.20 mg/kg dose, which instead of inducing a complete psychedelic experience, would induce some pharmacological effects, acting as an active placebo. The therapist and the patient were blind to the dose of ketamine received. Both groups improved in most of the areas evaluated (anxiety, depression, syndrome of anhedonia, etc.) overall, but the rate of abstinence after 24 months was significantly higher in the high dose group compared to that of the low dose group, and no significant adverse reactions were reported.

Psilocybin

Psilocybin has been widely studied for the treatment of addiction and treatment-resistant depression, as demonstrated on the study by Bogenschutz et al. (2015). The single-group, within-subjects design study evaluated a total of 10 participants with alcohol dependence from 25 to 56 years old, 4 women and 6 men that received a 12-week, 14-session manualized intervention, which included two open-label psilocybin sessions, and outcome data was collected for 36 weeks in total. A significant improvement in drinking was observed with large pre-post effect sizes, as well as improvement in the psychological measures relevant to drinking, much of this improvement occurring after the administration of psilocybin, and after four weeks of psychosocial treatment and 4-6 hours of assessment. The sample size in this study was its most important limitation, as well as the lack of a control group.

The open-label clinical trial made by Carhart-Harris et al. (2017) focused on changes in brain function before versus after psilocybin in patients with treatment-resistant depression who received two doses of the drug, 10 mg followed by 25 mg 1 week apart. Nineteen patients diagnosed with treatment-resistant major depression were enrolled and assessed with the Quick Inventory of Depressive Symptomatology-Self Report (QIDS-SR16) pre-treatment and post-treatment, and the results demonstrated a rapid and sustained antidepressant effect, with only one patient not showing a decrease in the QIDS-SR16 score.

Another study with psilocybin was conducted by Carhart-Harris et al. (2018), in which 20 patients with treatment-resistant depression received two doses of psilocybin, (10 and 25 mg, 7 days apart) while also underwent through psychological support, and the results were a fast and sustained response in the reduction of anxious and depressive symptoms, that remained significative after a 6 month follow-up, as could be evaluated in their QIDS-SR 16 (Quick Inventory of Depressive Symptoms) scores.

A randomized 2-session double-blind cross-over trial made by Griffiths et al. (2016) was conducted in regard to cancer patients with anxiety and/or depression. Fifty-one participants with life-threatening cancer diagnosis (breast, upper aerodigestive, gastrointestinal, genitourinary, hematologic and others) and a DSM-IV diagnosis of anxiety or mood symptoms were assigned randomly to one of two groups: low-dose-1st group, in which participants received a low dose of psilocybin on the first session, and a low dose on the second session, and the high-dose-1st group, which received the high dose first. The two primary therapeutic outcome measures were the clinician-rated measures of depression, the Grid Hamilton Depression Rating Scale (GRID-HAM-D-17) and HAM-A, assessed with the Structured Interview Guide for the Hamilton Anxiety Scale (SIGH-A). Psilocybin produced a large, sustained effect on the 2 primary outcome measures, as well as in most of the secondary measures assessed at baseline, 5 weeks after each session, and at 6-month follow-up, with an overall rate of clinical response at 6 months of 78% on clinician-rated depression and 83% on anxiety, thus increasing an improvement in the quality of life of the affected patients.

The randomized controlled trial by Agin-Liebes et al. (2020), compared single-dose psilocybin with

single-dose niacin along with psychotherapy in 14 patients with cancer-related adjustment disorder with anxious or depressed features or generalized anxiety disorder. The primary measures utilized were: Hospital Anxiety and Depression Scale (HADS) total scores (HADS-T), for anxiety (HADS-A) and for depression (HADS-D), BDI-II, STAI-T and STAI-S. Participants were randomly assigned to one of two groups, one group received psilocybin (0.3mg/kg) on the first medication session, followed by niacin (250 mg) on the second session, while the other received the niacin first. Statistically significant reductions relative to baseline on all primary measures regarding anxiety and depression at the 6.5 month, first and second follow-up. The percentages of clinical responses for depression as assessed by HADS-D and BDI ranged from 57-79% and depression symptom remission rates ranged from 50-79% at the second follow-up (4.5 years) and 71-100% of participants attributed positive life changes to the psilocybin -assisted therapy experience. Noteworthy limitations of this study are the small sample size, the impossibility to separate the effects of psilocybin from those of the psychotherapeutic sessions.

Ayahuasca

The parallel-arm double-blind randomized placebo-controlled trial conducted by Palhano-Fontes et al. (2019) tested the antidepressant action of ayahuasca in patients with treatment-resistant depression. A sample of 35 patients were allocated to either the ayahuasca treatment group (n=17) or placebo (n=18); but only 29 of them, 14 in the ayahuasca group and 15 in the placebo group could be analyzed. The primary outcome measure was the change in depression severity score as assessed by the HAM-D scale, comparing the baseline with 7 days after dosing. Patients in the placebo group received a 1 mL/kg liquid designed to simulate the taste and color of ayahuasca, and the ayahuasca group received the same quantity of ayahuasca. The ayahuasca used contained (mean ± S.D.) of 0.36 ± .01 mg/mL of N, N-DMT. The dosing sessions lasted for around 8 hours, and patients were asked to remain quiet, with closed eyes, and focusing on their body, thoughts and emotions, and they received support throughout the session from at least two investigators. Results reported a rapid antidepressant effect after a single dosing session with ayahuasca when compared with placebo. Depression severity improved significatively and overall psychiatric scales in the ayahuasca group were significatively higher than those in the placebo group in all time points after dosing. Patients reported nausea and approximately 57% vomited, but no other relevant side effects were reported. The most important limitation of this study was the size of the sample..

3,4-Methylenedioxymethamphetamine (mdma)

The only study in this review addressing the treatment of PTSD is also the only study made with the use of MDMA. The randomized double-blind, dose-response phase 2 clinical trial by Mithoefer et al. (2018) sought to assess the efficacy and safety of MDMA-assisted psychotherapy for the treatment of chronic PTSD in military veterans, firefighters and police officers. A sample of 26 veterans and first responders aged 18 or more, with PTSD and a CAPS-IV score of 50 or greater met eligibility criteria and were randomly assigned to receive 30 mg, 75 mg or 125 mg of MDMA orally in two 8-hour sessions with concomitant manualized psychotherapy. They were assessed with the use of the CAPS score. The results demonstrated that the groups that received 75 and 125 mg of MDMA with adjunctive psychotherapy in a controlled setting had significantly greater decreases in PTSD symptom severity in contrast of the 30 mg group. It is worth mentioning that 85 adverse events were reported by 20 participants, with four of them being serious, although three of them were deemed unrelated, and one possibly related to drug treatment.

Discussion

Most of the studies regarding the use of VR showed significative efficacy and proved these novel therapies to be useful. However, the size of the samples in some of the studies tend to be relatively small. For instance, the study made by Fowler et al. (2019) having the smallest sample (n=16). In the case of psychedelics, the most used drugs in the trials reviewed in the present manuscript were ketamine and psilocybin, although as in the case of VR therapies, the samples in some studies with psychedelics were quite small. The study by Bogenschutz et al. (2015) had the smallest sample (n=10). The results were positive in all of the studies with hallucinogens, with variations in the onset and duration of the effects, depending on the substances and dosages applied.

Our research identified various trials in which either VR assisted therapies or the use of psychedelics have been studied in order to decrease the symptomatology and increase the quality of life of people affected by psychiatric disorders, including those that pose a therapeutic challenge for clinicians, such as schizophrenia (du Sert et al., 2018). Unfortunately, our research yielded less information than we expected, as not many trials have been made with the use of both VR and psychedelics.

The pathologies addressed in studies reviewed were not diverse, nor were the substances employed in the trials with hallucinogens. No studies were found focusing on gender dysphoria or OCD, either with VR or psychedelics. More information regarding VR-assisted therapies was readily available, and still, the sample sizes and the variability of the level of immersion depending on the hardware and software used on the trials may have posed a negative impact on outcomes, as is the case of the study of Bouchard et al. (2017), in which 9 of the treatment sessions were not recorded because of technical issues. Information about research with psychedelics is scarcer and often repetitive, but that is expected because of the great taboo and potential of misuse surrounding these substances, as well as the lack of legal availability of most of them (Byock, 2018).

Both VR and psychedelic assisted therapies were found to be safe and effective, with little or no side-effects during or after the therapy sessions. Trials with ketamine and the trial with MDMA by Mithoefer et al. (2018) had the most important adverse reactions related to physiological distress, but these reactions were temporary and less meaningful than the overall benefits of the therapies in which they were used. All of the studies yielded a statistically significant improvement of the symptoms and quality of life of the patients, even in cases with treatment-resistant disorders, but most studies consist of very small samples and some of them did not count with a control group or in some cases, the control group was also too small (Bogenschutz et al., 2015; Fowler et al., 2019), which may have an

important impact on the final results. Generally, both the use of VR and Psychedelics as an adjutant for the treatment of psychiatric pathology show promising results, however, experimental research in these topics is scarce, and requires studies with bigger samples and higher statistical power in order to start thinking of these therapies not only as an adjutant therapy.

VR-assisted therapies offer numerous benefits, both for the clinician and the patient, highlighted by most authors cited in this paper, such as: availability, the potential of being used in a more ecological way, and the possibility of molding the virtual environment according to the specific pathology and needs of the patient (Aminov et al., 2018; Botella et al., 2015; Clus et al., 2018; de Carvalho et al., 2017). VR technologies hold a great potential for future use, but the development of software specifically made for therapeutic means needs to be encouraged, as the technological development is often outshined by the entertainment industry (Riva et al., 2019).

As for the use of psychedelics, due to the legal context in many countries (Byock, 2018), specially developing countries, research with hallucinogens is not easily performed, which might explain why a great part of the trials included in our results utilized ketamine, as it is a drug that is already used in hospitals, and is not very difficult to obtain in that context (Krupitsky et al., 2002; Nowacka & Borczyk, 2019). Research with the use of psilocybin and other psychedelics is once again starting to gain importance, but it needs to be further developed and improved in order to exploit the full potential that they pose in order to recreate therapeutics for mental disease, and even offer relief or at least alternatives for the support of people affected by conditions such as gender dysphoria or obsessive-compulsive disorder (Agin-Liebes et al., 2020; Thomas et al., 2017).

Although no manuscript targeting the experimental use of both VR and psychedelics along with psychological support were found in our research, we believe that a trial with the use of both methods should be attempted. Optimistically speaking, both of the aforementioned therapies have proven useful and have yielded statistically significant results overall. In this sense, both strategies may produce a synergic effect in patients with a specific psychiatric disorder if they receive an early treatment (Aday, Davoli, & Bloesch, 2020). The possibilities are endless, but once again, we encourage the development of much needed further research in these topics.

Conclusion

According to the evidence found and analyzed, VR showed security and significant efficacy in the management of special cases of phobias (social, motion pain and spiders), eating disorder, PTSD, gambling disorder, preoperative anxiety and schizophrenia. The hallucinogen drugs evaluated in the present systematic review exhibited positive effects in the treatment of depressive and anxiety disorders, alcohol dependence and PTSD. In general, hallucinogens produced mild adverse reactions during the studies. More research is needed in order to test the effectiveness of these therapies in different mental illnesses and different populations (children, adolescents, adults, elderly, men, women, etc.)

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