

ORIGINAL

ALCO-VR Project: A randomized clinical trial evaluating virtual reality cue-exposure Therapy for Treatment-Resistant Alcohol Use Disorder patients

Proyecto ALCO-VR: Un ensayo clínico aleatorizado para la evaluación de la eficacia de la Terapia de Exposición a Señales con Realidad Virtual en pacientes resistentes al tratamiento diagnosticados con trastorno por uso de alcohol

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Abstract

The management of “treatment-resistant” alcohol use disorder (AUD) often presents significant challenges. Virtual reality (VR) applications, specifically VR cue exposure therapy (VR-CET), offer a potentially complementary approach to the standard treatment (TAU). This randomized clinical trial (RCT) aimed to assess VR-CET’s effectiveness when added to TAU, compared to TAU alone, in reducing alcohol craving and anxiety among individuals with treatment-resistant AUD. The study also sought to determine anxiety and craving levels during VR-CET sessions and to explore long-term effects.

Eighty-five AUD patients from the Clinic Hospital of Barcelona participated. They were randomly assigned to either an experimental group (EG), receiving VR-CET plus TAU, or a control group (CG), receiving TAU alone. The EG completed six VR-CET sessions alongside TAU, while the CG continued with only TAU. Alcohol craving and anxiety were assessed before and after treatment for both groups, and during VR-CET sessions for the EG. Relapses were monitored at 3-, 6-, and 12-months post-treatment. Results indicated no significant main effects of “type of treatment” (EG vs. CG) on craving or anxiety. However, a significant “time” factor was observed, showing reductions in craving and anxiety from pre-test to post-test, regardless of the treatment type. Within VR-CET sessions, EG participants reported minimal anxiety and craving by the end of the therapy. Importantly, no statistically significant differences in relapse rates were found between the EG and CG at any follow-up period (3, 6, 12 months). The clinical implications of the study, limitations, and research directions are further discussed.

Keywords: alcohol use disorder, alcohol craving, anxiety, virtual reality, cue-exposure therapy, clinical trial

Resumen

El manejo del trastorno por consumo de alcohol (TCA) resistente al tratamiento presenta desafíos. La terapia de exposición a señales con realidad virtual (TES-RV) es un enfoque complementario al tratamiento estándar (TE). Este ensayo clínico aleatorizado (ECA) evaluó la eficacia de TES-RV con TE, comparado con TE solo, para reducir craving y ansiedad por el alcohol en pacientes con TCA resistente. También buscó determinar niveles de craving y ansiedad durante las sesiones de TES-RV y explorar efectos a largo plazo en la abstinencia. Participaron 85 pacientes con TCA del Hospital Clínic de Barcelona. Fueron asignados aleatoriamente a un grupo experimental (GE), con TES-RV más TE, o a un grupo control (GC), solo con TE. El GE completó seis sesiones de TES-RV junto con TE; el GC continuó solo con TE. Se evaluaron craving y ansiedad por el alcohol antes y después del tratamiento en ambos grupos, y durante las sesiones de TES-RV en el GE. Las recaídas se monitorizaron a los 3, 6 y 12 meses post-tratamiento. Los resultados no mostraron efectos significativos del tipo de tratamiento (GE vs. GC) sobre craving ni ansiedad. No obstante, un factor temporal significativo indicó reducciones en craving y ansiedad del pretest al posttest, independientemente del tratamiento. Durante las sesiones de TES-RV, los participantes del GE reportaron niveles mínimos de craving y ansiedad al finalizar. No se hallaron diferencias estadísticamente significativas en las tasas de recaída entre el GE y el GC en ningún seguimiento. El estudio discute implicaciones clínicas, limitaciones y futuras líneas de investigación.

Palabras clave: trastorno por consumo de alcohol, deseo por alcohol, ansiedad, realidad virtual, terapia de exposición a señales, ensayo clínico

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Current research indicates that alcohol use disorder (AUD) is a result of a continuous pattern of alcohol misuse (Kranzler & Soyka, 2018; Kuntsche et al., 2017; Morean et al., 2018; Witkiewitz et al., 2017). In addition to the personal circumstances of the individual, several underlying mechanisms facilitate the maintenance of AUD such as the interplay between *affective mechanisms* [e.g., stress and anxiety] (Anker et al., 2018; McCaul et al., 2017) and *alcohol craving*, described as an intense urge to drink alcohol (Bernard et al., 2021; Drummond, 2001; Manchery et al., 2017).

The AUD treatment in public health care settings, known in the literature as treatment as usual (TAU), consists of pharmacological and psychosocial interventions (Mann & Hermann, 2010). Pharmacological interventions include medication such as disulfiram, naltrexone, or acamprosate among others (Kranzler & Soyka, 2018). Psychosocial treatment approaches reflect interventions that address the psychological and social elements that contribute to mental health disorders. Such interventions may include individual therapy and support groups. The psychotherapeutic approach is based on the principles of cognitive-behavioral therapy (CBT) and other interventions related to behavior change such as motivational interviewing (Witkiewitz et al., 2019). However, long-term effect of both pharmacological and psychosocial interventions for AUD is modest. While some studies have shown that TAU can be effective (Naqvi & Morgenstern, 2015), others have found that few patients complete treatment successfully (Patterson Silver Wolf et al., 2021; Patterson Silver Wolf et al., 2019). In this sense, approximately 40% of individuals experience relapse during/after treatment (Andersson et al., 2019). Patients with AUD who experience relapse are often given the same treatment options as before, which leads to a revolving door of treatment (Naqvi & Morgenstern, 2015; Patterson Silver Wolf et al., 2021). Treatment-resistant AUD is a chronic condition characterized by a return to drinking patterns after treatment completion and/or difficulty to complete treatment (Patterson Silver Wolf et al., 2022). Considering the ongoing concern regarding recovery management, new treatment options are the focus of the latest research in AUD.

Virtual reality (VR) technology is increasingly being used to improve the treatment of different disorders, including addictions. In AUD, it has been used primarily as a method of conducting cue-exposure therapy (CET), which involves repeated and prolonged (*in vivo*, imagining or multimedia) exposure to alcohol beverages by presenting alcohol-related cues with the aim to prevent drinking-related behaviors (Ferrer-García et al., 2017). Nonetheless, the effectiveness of CET in addressing AUD remains a topic of contention, as evidenced by studies such as Byrne et al. (2019) and Mellentin et al. (2017). In this context, a recent meta-analysis revealed that CET has a small to moderate impact

on factors such as daily alcohol consumption, total days of drinking, and AUD relapse. However, it is important to note that the quality of evidence supporting these findings is rated as low, as indicated by Kiyak et al. (2023). The VR-based therapeutic approach leverages the fundamental mechanism of CET, which is systematic desensitization, as outlined by Conklin and Tiffany (2002). Its objective is to systematically and gradually expose individuals to decrease their psychophysiological responses to cues related to alcohol (Mellentin et al., 2016).

VR poses several advantages such as digital simulations of real-life situations: VR adds effectiveness to CET because technology enables induction of greater subjective and physiological reactivity (e.g. craving). The user is immersed within the VR-environment, therefore feeling “present” while staying in a safe, secure, yet more flexible approach than those from *in vivo* contexts. VR also allows a greater control of the input variables, thus providing a more ecological approach that eases the generalization of treatment effects to real-world and daily life situations (Ghiță & Gutiérrez-Maldonado, 2018; Hone-Blanchet et al., 2014; Parsons, 2015; Segawa et al., 2020; Simon et al., 2020). This is translated into a recent study indicating that VR-based interventions are effective in preventing smoking relapses (Malbos et al., 2023). Consequently, the combined approach of VR and CET has emerged as VR-CET.

Previous systematic reviews endorse and support the application of VR in alcohol misuse, for both CET and other purposes (i.e., examining relationships between alcohol and neurological activity, or training for healthcare professionals), but the relevance of findings is limited and frequently based on methodological flaws, facts that highlight the importance of further empirical research (Durl et al., 2017; Ghiță & Gutiérrez-Maldonado, 2018; Trahan et al., 2019). Finally, although VR has shown promising short-term results, further longitudinal research is needed to evaluate the effects of CET using VR in patients with AUD (Durl et al., 2017).

The present study is part of a comprehensive project that investigates the use of VR for the treatment of AUD. The software employed in this study, referred to as “ALCO-VR”, was developed based on the findings of earlier research within the project. The initial study in the project aimed to identify alcohol-related cues and contexts that trigger cravings, with the goal of creating virtual environments with clinical relevance (Ghiță et al., 2019a). The study’s results highlighted that the most frequent alcohol-related contexts included bars, restaurants, pubs, and home environments. Patients self-reported a wide range of alcoholic beverages, leading to the development of a library featuring 22 different alcoholic drinks within the VR platform. The second study in the project emphasized the development and validation of the “ALCO-VR” platform (Ghiță et al., 2019b). Data from this study revealed that VR environments

related to alcohol induced greater anxiety and alcohol craving responses among patients with AUD compared to a control group consisting of social drinkers. These studies determined that TAU + VR-CET outweighed TAU alone, and they highlighted a bidirectional relationship between AUD severity, perceived realism of virtual environments and beverages, and alcohol craving.

The main objectives of the current study were: 1) To evaluate the efficacy of VR-CET + TAU (experimental group -EG-) in comparison to TAU alone (control group -CG), in reducing levels of alcohol craving and anxiety after treatment in individuals diagnosed with AUD who were considered resistant to treatment; 2) To analyze momentary levels of alcohol craving and anxiety during VR-CET (intra-session assessment) in the EG; 3) To explore long-term effects of VR-CET versus TAU at follow-up timepoints (3, 6, and 12 months) after treatment completion, in reducing the percentage of relapses.

To address these objectives, the following hypotheses were formulated: 1) The EG will report a greater reduction in anxiety and alcohol craving compared to the CG after treatment; 2) The EG will report a gradual reduction in momentary levels of alcohol craving and anxiety during the VR-CET sessions; 3) EG will report a lower percentage of relapses compared to CG at follow-up timepoints (3, 6, and 12 months) after the treatments.

Methods

Study design

A single center, two-arm, single-blind RCT was conducted with the aim of determining the efficacy of VR-CET + TAU compared to TAU only for the treatment of AUD. Consecutive sampling was employed as the recruitment method for selecting participants in this study. The study was performed in accordance with the Declaration of Helsinki (World Medical Association, 2001). Ethical approval was obtained from the Ethics Committees of both the University of Barcelona and Hospital Clinic of Barcelona, Spain [ethical code number: 0377 (HCB/2017/0377); approval date: 09/2017]. The study protocol identifier on ClinicalTrials.gov is NCT04858061. Deviations with respect to the initial intended research plan were stated, since the follow-up finally consisted solely in requesting the subject on his/her maintenance of abstinence at three different timepoints (3, 6 and 12 months), but no self-report evaluations on alcohol craving and anxiety were collected. Follow-up was hindered by the low adherence obtained across subjects, alongside the outbreak of the Covid-19 pandemics, a fact that induced and led to the development of the follow-up sessions by telephone.

Participants

Considering an effect size of 0.5, alpha set at 0.05, and 0.80 statistical power (Faul et al., 2007), the sample size required was $N = 84$. The predetermined effect size (ES), as assessed by Cohen's d , was set at 0.5. This implies that the difference between the means of the groups is equal to half the standard deviation of the groups. The choice of a pre-established effect size of 0.5 was informed by the typical effect sizes observed in meta-analyses within the field of psychology, which tend to hover around $d = 0.50$ (Bakker et al., 2012; Sullivan & Feinn, 2012). Power size calculation was run with G*Power version 3.1.9.7 (Faul et al., 2007). The recruitment process was extended to reach a total of 100 participants, due to the relatively high dropout rates typically encountered in these studies.

A total of 100 participants were initially assessed for eligibility from the outpatient clinic of the Addictive Behaviors Unit of the Hospital Clinic of Barcelona. The study's inclusion criteria encompassed adults aged 18 and older diagnosed with AUD as per DSM-5 guidelines (American Psychiatric Association, 2013), who had experienced at least one relapse episode within the first six months following a prior hospital treatment and had refrained from alcohol consumption for at least three days preceding the initial session. Exclusion criteria included severe cognitive impairment that could impede study completion, use of anti-craving medication (e.g., naltrexone), severe psychopathological conditions (e.g., major depression, psychosis), epilepsy, pregnancy, or severe visual impairments. Occasional substance use, such as tobacco or cannabis, was permitted. Fifteen participants

did not meet the eligibility criteria and, consequently, were not included in the study. The specific reasons for exclusion were that they declined to participate in the study (13 participants) and had severe visual impairments (2 participants). The remaining participants ($N = 85$, $M_{\text{age}} = 52$, $SD = 9.2$), underwent randomization and were, subsequently, randomly allocated to one of the two groups: EG ($N = 37$) and CG ($N = 48$). Among these, 18 participants completed the EG treatment, while 33 participants completed the CG treatment (Figure 1).

Simple randomization was employed, where each participant was assigned to a treatment group with a known (typically equal) probability, without consideration of the treatment assigned to other participants in the study. This allocation was determined through a coin toss (Kang et al., 2008; Suresh, 2011).

Measures and materials

Alcohol Use Disorder Identification Test (AUDIT) (Contel et al., 1999) was used to determine problematic drinking-behavior patterns. AUDIT consists of 10 items scoring from 0-to-4. The final score ranges from 0 to 40 points. A final score equal to or higher than 8 points is the

cut-off score to indicate hazardous drinking and warrants further assessment for possible AUD. In our study, AUDIT was also used as a severity indicator of AUD, as seen in previous research (Donovan et al., 2006). The psychometric properties of this instrument have been widely validated (Babor et al., 2001).

Multidimensional Alcohol Craving Scale (MACS) (Guardia-Serecigni et al., 2004) was used to detect the intensity of alcohol craving in the past week. MACS consists of 12 Likert-based items with possible scores in a 1-to-5 range (“strongly disagree to strongly agree”). Its outcome categories are non-existent (score 12-19), mild (13-22), moderate (23-40), or intense (>40) craving. An example of an item is “The urge to drink has been very intense”. This scale has demonstrated a strong internal consistency with $\alpha = 0.94$ (Guardia-Serecigni et al., 2004) and a good sensitivity to detect changes in alcohol consumption (Guardia-Serecigni et al., 2006). The internal consistency of the instrument was calculated in our study, displaying Cronbach’s alpha values of 0.869 for the 12-item tool.

Figure 1
Flowchart of the RCT

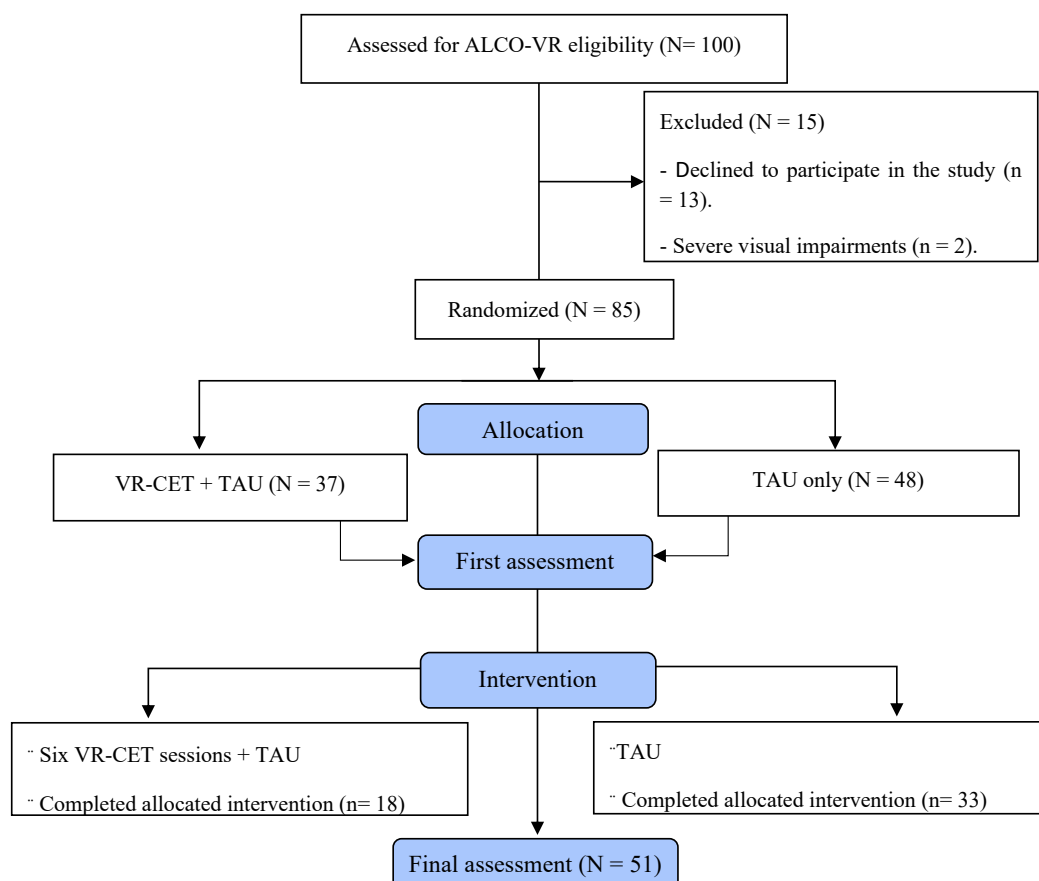
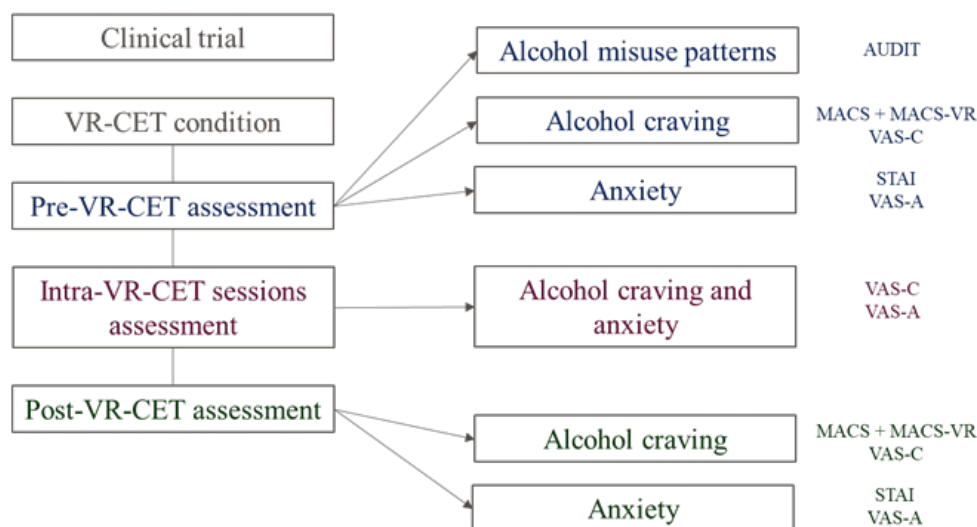


Figure 2
Assessment procedure in the ALCO-VR study



*Note. The initial and final assessment sessions were the same for both groups, however the intra-VR session assessment was conducted only in the EG.

Multidimensional Alcohol Craving Scale – Virtual Reality (MACS-VR) was an ad-hoc modified version of the original MACS (with the same items and outcomes) to assess alcohol craving immediately after VR exposure. The items, the scoring part, and interpretation were the same as in the original MACS. The only modification we made concerned the instructions of the questionnaire. Instead of determining alcohol craving in the *last week* as depicted in the instructions of MACS, the aim of MACS-VR was to report alcohol craving *immediately after exposure to the VR environments*. The internal consistency of the MACS-VR was assessed in the current study, with Cronbach’s alpha values of 0.920 for the aforementioned instrument.

State-Trait Anxiety Inventory (STAI) (Spielberger et al., 1982) cross-cultural research. The State-Trait Anxiety Inventory (Spielberger, et al., 1970) is a self-reported scale with two-subscales (state-anxiety and trait-anxiety) of 20 items each, and scores for each item range from 0 to 3. The psychometric properties have been extensively analyzed in relation to internal consistency, test-retest reliability and obtaining consistent evidence of validity (Bados et al., 2010; Guillén-Riquelme & Buela-Casal, 2011; Mystakidou et al., 2009).

Ad-hoc assessment item of alcohol consumption was created to explore alcohol use (relapse) at 3-, 6-, and 12-month follow-ups. The dichotomous item “*Have you consumed any alcohol since....?*” had two possible answers (yes/no).

Visual Analog Scales (VAS) for craving (**VAS-C**) and anxiety (**VAS-A**) were used to measure momentary levels of alcohol craving and anxiety during VR exposure, with scores ranging from 0 to 100. An example of the VAS-C was “On a scale from 0 to 100, please rate your momentary level of alcohol craving”. A similar item was used to measure anxiety on VAS-A: “On a scale from 0 to 100, please rate your momentary level of anxiety”.

Procedure

Patients were recruited during their participation in TAU at the Addictive Behaviors Unit of the Clinic Hospital of Barcelona (Barcelona, Spain). Written informed consent was obtained before their inclusion in the study. Subsequently, participants were randomly allocated to either the EG, receiving TAU and VR-CET, or the CG, which received only TAU (see Figure 2).

The ALCO-VR software is named after the project itself. Its development (Ghiță et al., 2019a), clinical implications (Ghiță et al., 2019b), and clinical applications (Hernández-Serrano et al., 2020; Hernández-Serrano et al., 2021) have been detailed in other publications. The VR equipment included an Oculus Rift S head-mounted display (HMD), sensors, touch controllers, and a computer compatible with VR technology. The ALCO-VR software encompassed two components: assessment and therapy. Regarding the assessment, all participants underwent

Figure 3

Images of the four alcohol-related VR environments (restaurant, at-home, pub, and bar)



two assessment sessions (prior to and following TAU + VR-CET or TAU protocols). The initial assessment session (pre-treatment) involved a clinical interview, which gathered sociodemographic data, including the patient's AUD history, use of substances other than alcohol, dual diagnosis, and abstinence status. It also included two assessment methods: 1) assessment via the ALCO-VR software (utilizing VAS-C and VAS-A); 2) assessment using paper-and-pencil instruments (comprising AUDIT, STAI-State, STAI-Trait, MACS, MACS-VR, and evaluations of perceived realism during VR assessment). The VR assessment with ALCO-VR software involved establishing a hierarchy of exposure, progressing from the lowest-rated environment with the lowest-rated alcoholic drink to the highest-rated environment and the highest-rated alcoholic drink in terms of alcohol craving. Prior to the VR alcohol-related experience, the software introduced a neutral environment, consisting of a white room with a glass of water, designed to familiarize users with VR technology. The system enabled users to select their preferred alcoholic beverages and create a hierarchy based on their self-ratings of alcoholic drinks and environments. Subsequently, participants were exposed to each of their top five favorite drinks for 20 seconds in each of the four VR environments (bar, pub, restaurant, and at-home settings). The paper-

and-pencil questionnaire assessment included STAI-State and MACS, administered prior to the VR assessment, while STAI-Trait, MACS-VR and perceived levels of realism were completed immediately after the VR assessment. However, AUDIT was only conducted before the VR assessment. A final assessment session (post-intervention) occurred 3-4 weeks later, employing the same instruments, excluding the clinical interview, AUDIT, and perceived levels of realism.

Regarding therapy, only the EG received six VR-CET booster sessions employing the ALCO-VR software, in addition to TAU. These booster sessions solely involved cue-exposure. During the sessions, patients interacted with the VR environment by handling alcoholic beverages and inspecting them from all angles without attempting to drink. VR-CET sessions comprised exposure to the most preferred alcoholic drinks within the four VR environments (pub, bar, at-home, and restaurant), conducted twice a week for three weeks (see Figure 3). The VR-CET approach involved gradual exposure from the lowest-rated to the highest-rated alcoholic drinks and VR environments in terms of alcohol craving. The ALCO-VR software encouraged participants to progress to the "next level" only if they scored 40% less anxiety and craving, three times in a row, than their initial ratings. Depending on the self-ratings of alcohol craving

and anxiety, the patient was either exposed again to the same alcohol drink and environment or allowed to move to the “next level”. “Next level” implied the exposure to a new alcohol drink from the five initially chosen ones. A similar procedure was implemented in all the six VR-CET sessions.

The CG did not receive VR-CET sessions and continued with their TAU. Participants in both the CG and the EG underwent the same baseline treatment, which consisted of standard treatment at the Hospital Clinic of Barcelona. Treatment encompassed a combination of pharmacotherapy and psychotherapy: 1) Pharmacotherapy typically included medications such as disulfiram, anxiolytics, and/or antidepressants; 2) Psychotherapy involved individual and group therapy sessions grounded in psychotherapeutic approaches like cognitive-behavioral therapy and motivational interviewing. Components of the psychotherapeutic approach were psychoeducation, addressing maladaptive cognitive styles and underlying core beliefs, behavioral activation, coping skills training, social support, as well as incorporating the stages of behavioral change. Weekly group sessions involved guided recovery-oriented discussions in an open-group format, meeting once or twice weekly for 1 hour and 30 minutes. All patients received TAU, however, it is important to mention that the VR exposure protocol was administered only to the participants in the experimental condition (EG). Participants in the TAU condition (CG) underwent two assessment sessions only, with a 4–5-week gap between them.

During the VR exposure, olfactory stimuli were employed to enhance the realism of the environments. A small quantity of an alcoholic beverage, matching those observed during VR exposure, was applied to cotton pads and placed in proximity to each participant. Assessment and therapy sessions had an approximate duration of one hour. The VR-CET treatment was administered by experienced research-practitioners with both clinical and research backgrounds. The TAU treatment was administered by the regular therapists at the hospital.

Follow-up measurement of abstinence maintenance/recovery management were performed at three different timepoints (3, 6 and 12 months).

Statistical analyses

Normality was assessed using Shapiro-Wilk tests and Q-Q plots, and parametric/non-parametric tests were subsequently adopted when the assumptions of normality were not met. Baseline variables were compared using independent samples t-tests. For participants who completed the protocol ($N_{\text{Total}} = 51$; $N_{\text{TAU}} = 33$; $N_{\text{VR-CET + TAU}} = 18$), data from the initial and final assessment sessions were utilized to assess the efficacy of VR-CET. Consistency (psychometric property measuring the extent to which several items that

propose to measure the same general construct produce, indeed, similar scores) of the instruments MACS and MACS-VR was tested by means of Cronbach’s alpha, a statistic calculated from the pairwise correlations between items: a value of around 0.7 or greater is generally accepted as an indicator of high or good consistency (Cohen et al., 2007).

To evaluate the comparative effects of both treatments through time, a 2x2 Analysis of Variance (ANOVA) was performed, with the aim of assessing the parameters corresponding to the main effects of the treatment, those corresponding to temporality (with Bonferroni adjustment in the estimated marginal means of the dependent variable for all level combinations of a set of factors), and the interaction between both factors. Also, effect sizes between pre and post treatment for both groups across the four different environments for VAS-C (craving) and VAS-A (anxiety) were calculated by means of the statistic Hedge’s *g*. For the intra-session assessment of momentary levels of alcohol craving and anxiety (VAS-C, VAS-A), Wilcoxon signed-rank tests were employed to examine specific differences across the six VR-CET sessions, whilst trends and trajectories for the final scores of craving and anxiety (VAS-C and VAS-A, respectively) across the six sessions were defined through gender-based multilevel growth models, offering a more profound awareness of the dynamics of treatment through time in both genders (male/female), assessing linear relationships (equidistant timepoints) through Restricted Maximum Estimation Likelihood (RMEL) with fixed slopes and random intercepts (since this method has the advantage of being more parsimonious and less intense from a computational perspective than that with random slopes and intercepts) (Hedeker & Gibbons, 2006; McCormick, 2021; Steele, 2008). Relapses registered at 3-, 6-, 12-month follow-ups were registered and compared through Chi-square tests across the total sample, the EG, and the CG. Analyses were performed using IBM SPSS Statistics for Windows, Version 28.0 (Armonk, NY, USA: IBM Corp, 2021), with a p-level of significance set at $p < 0.05$.

Results

Baseline characteristics of the sample

Baseline characteristics are presented in Table 1. A total of 85 AUD patients, of which 60% were males, with a mean age of 52 years ($SD = 8.83$; age range: 32-to-69), participated in the study. There were no statistically significant differences between the groups in terms of baseline characteristics. According to AUDIT scores, patients exhibited moderate to severe drinking patterns ($M = 16.09$; $SD = 9.77$), and their alcohol craving was assessed as moderate [MACS ($M = 22.96$; $SD = 10.95$) and MACS-VR ($M = 26.33$; $SD = 13.02$)]. Anxiety levels, as measured

Table 1
Baseline patient characteristics and data from the first assessment session (N = 85)

Baseline characteristics	VR-CET + TAU (N = 37)		TAU (N = 48)		Group comparison p value
	M/(N)	SD/(%)	M/(N)	SD/(%)	
Age	52.33	9.35	52.42	9.19	.96
Gender					.72
Female	14	37.8	20	41.7	
Male	23	62.2	28	58.3	
Marital status					.43
Married/in a relationship	19	51.4	21	43.8	
Divorced/separated	9	24.3	14	29.2	
Single	3	8.1	10	20.8	
Other (e.g., widower)	3	8.1	3	6.3	
Education					.81
Elementary school	4	10.8	6	12.5	
High school	6	16.2	10	20.8	
Junior college	10	27.0	8	16.7	
University degree (BSc, MSc)	17	46	24	50.1	
Socio-economic resources					.24
Low	4	10.8	10	20.8	
Medium	32	86.5	37	77.1	
High	1	2.7	1	2.1	
Comorbid psychopathology					.60
None	21	56.8	26	54.2	
Depressive disorders	6	16.2	12	25.2	
Depressive and anxiety disorders	4	10.8	3	6.3	
Depressive, anxiety and personality disorders	0	-	2	4.2	
Anxiety disorders	1	2.7	2	4.2	
Personality disorders	5	13.5	3	6.3	
Medication					.75
No medication	14	37.8	20	41.7	
Antidepressants	8	21.6	9	18.8	
Anxiolytics	7	18.9	5	10.4	
Antipsychotics	1	2.7	1	2.1	
Combination of medication	7	18.9	13	27.1	
Disulfiram					.19
No	23	62.2	23	47.9	
Yes	14	37.8	25	52.1	
Smoking patterns					.09
No currently smoking	14	37.8	27	56.3	
Currently smoking	23	62.2	21	43.8	
Use of other substances					.13
No use	23	62.2	37	77.1	
Yes (e.g., illicit drugs)	14	37.8	11	22.9	
Abstinence (in days)	74	95	96	115	.34
Baseline data (first assessment)	N = 37		N = 48		p Value
	M	SD	M	SD	
Questionnaires and ad-hoc items					
AUDIT	15.38	10.90	16.58	8.97	.58
MACS	22.96	9.89	22.95	10.92	.99
MACS-VR	28.96	13.04	24.52	12.82	.13
STAI – Trait subscale	25.33	12.70	28.06	10.47	.29
STAI – State subscale	20.72	11.57	18.97	10.41	.48
VR assessment					
VAS-C (0-100)					
Neutral environment (water)	11.63	22.91	18.72	21.36	.21
At-home	50.39	29.25	45.62	33.09	.55
Bar	39.43	28.17	41.74	30.59	.75
Restaurant	38.90	27.23	37.70	28.49	.86
Pub	41.23	27.72	41.59	30.72	.92
VAS-A (0-100)					
Neutral environment (water)	22.23	26.49	20.55	24.05	.57
At-home	48.06	31.64	43.29	31.17	.55
Bar	38.43	27.17	35.23	29.16	.65
Restaurant	37.72	26.53	32.70	26.17	.46
Pub	40.57	27.05	37.11	26.97	.61

AUDIT, Alcohol Use Disorder Identification Test; **Disulfiram**, is common pharmacotherapy for the treatment of alcohol use disorder and is usually combined with other medications (e.g. antidepressants) depending on the condition of the patient; **MACS**, Multidimensional Alcohol Craving Scale; **MACS-VR**, Multi-dimensional Alcohol Craving Scale – Virtual Reality; **STAI**, State and Trait Anxiety Inventory; **VAS-A**, visual analog scale – anxiety; **VAS-C**, visual analog scale – craving; **Use of other substances**, patients self-reported occasional use of illicit substances like cannabis in the month prior to their inclusion in the study; **VR assessment**, virtual reality assessment.

by the STAI-Trait subscale ($M = 26.95$; $SD = 11.43$) and STAI-State subscale ($M = 19.70$; $SD = 10.87$), were also in the moderate to severe range at baseline. Furthermore, there were higher levels of craving and anxiety in alcohol-related environments compared to the neutral one.

Effects of time, treatment and their interaction on craving and anxiety on MACS and STAI

A two-way ANOVA was conducted to determine to what extent treatment and time have an effect on “craving” (MACS and MACS-VR) and “anxiety” (STAI-State). Focusing on craving, there was no significant interaction between the effects of treatment and time (MACS: $F=0.008$, $p=0.931$; MACS-VR: $F=5.131$, $p=0.052$). Simple main effects showed that time played a significant role on MACS-VR ($F=7.880$, $p=0.020$), but not on MACS ($F=2.258$, $p=0.167$). Treatment had no significant effects, neither in MACS nor in MACS-VR. As for anxiety, no statistically significant interaction was stated ($F=0.258$, $p=0.624$). Simple main effects analysis on time showed significant differences ($F=14.002$, $p=0.005$). Treatment had no statistical significance whatsoever.

Effects of time, treatment and their interaction on craving and anxiety on VAS

Also, a two-way ANOVA was conducted to determine to what extent treatment and time have an effect on “craving” (VAS-C in four environments: home, bar, restaurant, and pub) and “anxiety” (VAS-A in the aforementioned four environments). Concerning craving, there was no significant interaction between the effects of treatment and time (p values in a 0.334-to-0.461 range). Simple main effects showed no statistically significant differences, neither in time (p values in a 0.356-to-0.600 range), nor in treatment.

As for anxiety, no statistically significant interaction was stated (p values in a 0.234-to-0.402 range), whilst simple main effects analysis did not show significant differences either on time (p values in a 0.221-to-0.426 range), or in treatment.

Table 2 provides data on the aforementioned treatment effects.

Table 3 displays the different effect sizes (Hedge's g) between pre and post treatment timepoints in both treatment groups across the four environments.

Intra-session treatment effects on craving (VAS-C) and anxiety (VAS-A) during the VR-CET treatment in each of the six sessions

In the experimental group (EG), Wilcoxon signed-rank tests revealed differences in self-reported momentary levels of alcohol craving during intra-session assessment on VAS-C between the highest value of craving and the final value of craving (end of VR-CET session) in each of the six sessions. These differences were statistically significant

in the first ($Mdn = 50$ vs $Mdn = 16.50$, $Z = -3.181$, $p < .001$), second ($Mdn = 33$ vs $Mdn = 3.50$, $Z = -2.934$, $p = .003$), third ($Mdn = 19.50$ vs $Mdn = 2$, $Z = -2.521$, $p = .005$), fourth ($Mdn = 19.50$ vs $Mdn = 2$, $Z = -2.201$, $p = .028$), fifth ($Mdn = 35.50$ vs $Mdn = 0$, $Z = -2.200$, $p = .028$), and sixth session ($Mdn = 14.50$ vs $Mdn = 0$, $Z = -2.201$, $p = .026$).

In terms of anxiety, Wilcoxon signed-rank tests revealed significant differences in self-reported momentary levels of anxiety during intra-session assessment on VAS-A between the highest value of anxiety and the final value of anxiety (end of VR-CET session) in each of the six sessions in the EG. These differences were statistically significant in the first ($Mdn = 49$ vs $Mdn = 11$, $Z = -2.934$, $p = .003$), second ($Mdn = 31.50$ vs $Mdn = 5.50$, $Z = -2.803$, $p = .005$), third ($Mdn = 41.50$ vs $Mdn = 1$, $Z = -2.524$, $p = .012$), fourth ($Mdn = 36$ vs $Mdn = 0$, $Z = -2.521$, $p = .012$), fifth ($Mdn = 14$ vs $Mdn = 0$, $Z = -2.371$, $p = .018$), and sixth session ($Mdn = 6$ vs $Mdn = 0$, $Z = -2.201$, $p = .028$). Intrasession changes of craving and anxiety are displayed in Figure 4.

Multilevel growth curves were used to assess trends and trajectories for the final scores of craving and anxiety (VAS-C and VAS-A, respectively) across the six sessions were defined through multilevel growth models for male/female participants, offering a more profound awareness of the dynamics of treatment through time in both genders. The model for VAS-C depicted a Schwartz's Bayesian Criterion (BIC) of 818.37, with estimates of fixed effects being not statistically significant, neither for time (95% Confidence Interval -95%CI: -10.812 – 3.954), nor for gender (95%CI: -20.398 – 24.446) or time*gender (95%CI: -6.448 – 3.501). The model concerning VAS-A displayed a BIC = 809.704, with the following non-statistically significant estimates of fixed effects: time (95%CI: -11.017 – 3.430), gender (95%CI: -19.173 – 20.595), time*gender (95%CI: -6.011 – 3.729). The graphical representation of the evolution of craving and anxiety through the six sessions of the EG displayed by gender is shown in Figure 5.

Relapses at follow-ups

Table 4 displays the relapse percentages registered at 3-, 6-, 12-month follow-ups. The Chi-square performed reported no statistically significant differences were observed between the EG and the CG in any of the three time-points assessed, with p -values ranging from 0.992 to 0.998.

Table 2
2*2 ANOVA (*Treatment*Time*)

2*2 ANOVA (Treatment, Time)							
	VR-CET+TAU		TAU		Principal Effect Treatment	Principal Effect Time	Interaction Treatment-Time
	Pre (n=37)	Post (n=16)	Pre (n=48)	Post (n=31)			
Craving							
MACS	22.96 ± 9.89	17.50 ± 9.75	22.95 ± 10.92	18.64 ± 7.77	F=1.021 p-value=0.339 Partial Eta²=0.102	F=2.258 p-value=0.167 Partial Eta²=0.201	F=0.008 p-value=0.931 Partial Eta²=0.001
MACS-VR	28.96 ± 13.04	16.18 ± 9.11	24.52 ± 12.82	20.35 ± 11.28	F=0.397 p-value=0.544 Partial Eta²=0.042	F=7.880 p-value=0.020* Partial Eta²=0.467	F=5.131 p-value=0.052 Partial Eta²=0.363
VAS-C							
Home	36.73 ± 26.75	7.21 ± 9.03	39.06 ± 30.97	38.53 ± 36.93	F=2.136 p-value=0.218 Partial Eta²=0.348	F=0.324 p-value=0.600 Partial Eta²=0.075	F=0.741 p-value=0.438 Partial Eta²=0.156
Bar	39.42 ± 28.17	6.85 ± 8.06	41.74 ± 30.59	34.33 ± 31.15	F=6.462 p-value=0.064 Partial Eta²=0.618	F=0.833 p-value=0.413 Partial Eta²=0.172	F=1.203 p-value=0.334 Partial Eta²=0.231
Restaurant	38.90 ± 27.23	7.78 ± 8.41	37.70 ± 28.49	36.13 ± 34.10	F=2.604 p-value=0.182 Partial Eta²=0.394	F=0.955 p-value=0.384 Partial Eta²=0.193	F=0.663 p-value=0.461 Partial Eta²=0.142
Pub	41.23 ± 27.72	8.00 ± 7.90	41.59 ± 30.72	36.13 ± 33.03	F=3.289 p-value=0.144 Partial Eta²=0.451	F=1.089 p-value=0.356 Partial Eta²=0.214	F=1.090 p-value=0.355 Partial Eta²=0.214
Anxiety							
STAI-State	20.72 ± 11.57	8.50 ± 8.16	18.97 ± 10.41	13.90 ± 8.51	F=3.110 p-value=0.112 Partial Eta²=0.257	F=14.002 p-value=0.005* Partial Eta²=0.609	F=0.258 p-value=0.624 Partial Eta²=0.028
VAS-A							
Home	35.74 ± 27.87	6.07 ± 9.97	36.73 ± 28.35	37.40 ± 34.22	F=1.126 p-value=0.348 Partial Eta²=0.220	F=0.785 p-value=0.426 Partial Eta²=0.164	F=0.878 p-value=0.402 Partial Eta²=0.180
Bar	38.43 ± 27.17	6.64 ± 9.95	35.23 ± 29.16	36.66 ± 27.39	F=5.872 p-value=0.073 Partial Eta²=0.595	F=1.189 p-value=0.337 Partial Eta²=0.229	F=1.965 p-value=0.234 Partial Eta²=0.329
Restaurant	37.71 ± 26.53	6.64 ± 9.14	32.69 ± 26.17	39.26 ± 34.65	F=1.375 p-value=0.306 Partial Eta²=0.256	F=2.101 p-value=0.221 Partial Eta²=0.344	F=1.472 p-value=0.292 Partial Eta²=0.269
Pub	40.57 ± 27.05	6.21 ± 8.64	37.11 ± 26.97	36.06 ± 31.58	F=2.713 p-value=0.175 Partial Eta²=0.404	F=2.089 p-value=0.222 Partial Eta²=0.343	F=1.761 p-value=0.255 Partial Eta²=0.306

MACS, Multidimensional Alcohol Craving Scale; MACS-VR, Multidimensional Alcohol Craving Scale – Virtual Reality; Perceived realism, the ad-hoc items were rated on a scale from 0 to 10; STAI, State and Trait Anxiety Inventory; TAU, treatment as usual; VAS-A, visual analog scale – anxiety; VAS-C, visual analog scale – craving; VR-CET, virtual reality cue exposure therapy; **p* < .05.

Table 3
Intragroup pre vs post Effect Sizes for VAS-C (craving) and VAS-A (anxiety)

	VR-CET+TAU			TAU		
	Pre (n=37)	Post (n=33)	Hedges' g	Pre (n=48)	Post (n=48)	Hedges' g
Craving						
VAS-C						
Home	36.73 ± 26.75	10.20 ± 11.69	1.28	39.06 ± 30.97	41.40 ± 26.75	0.01
Bar	39.42 ± 28.17	9.26 ± 10.34	1.35	41.74 ± 30.59	34.13 ± 31.12	0.24
Restaurant	38.90 ± 27.23	7.78 ± 8.41	1.33	37.70 ± 28.49	36.83 ± 34.90	0.05
Pub	41.23 ± 27.72	7.60 ± 7.96	1.40	41.59 ± 30.72	36.28 ± 33.24	0.17
Anxiety						
VAS-A						
Home	35.74 ± 27.87	6.11 ± 9.12	1.23	36.73 ± 28.35	27.90 ± 27.42	0.02
Bar	38.43 ± 27.17	6.64 ± 9.95	1.35	35.23 ± 29.88	36.66 ± 27.12	0.05
Restaurant	37.71 ± 26.53	6.64 ± 9.14	1.36	32.69 ± 26.17	39.88 ± 34.15	0.22
Pub	40.57 ± 27.05	6.88 ± 7.14	1.48	37.11 ± 26.97	35.76 ± 26.48	0.03

TAU, treatment as usual; VAS-A, visual analog scale – anxiety; VAS-C, visual analog scale – craving; VR-CET, virtual reality cue exposure therapy; * $p < .05$.

Figure 4
Momentary levels of alcohol craving reported on VAS-C and VAS-A

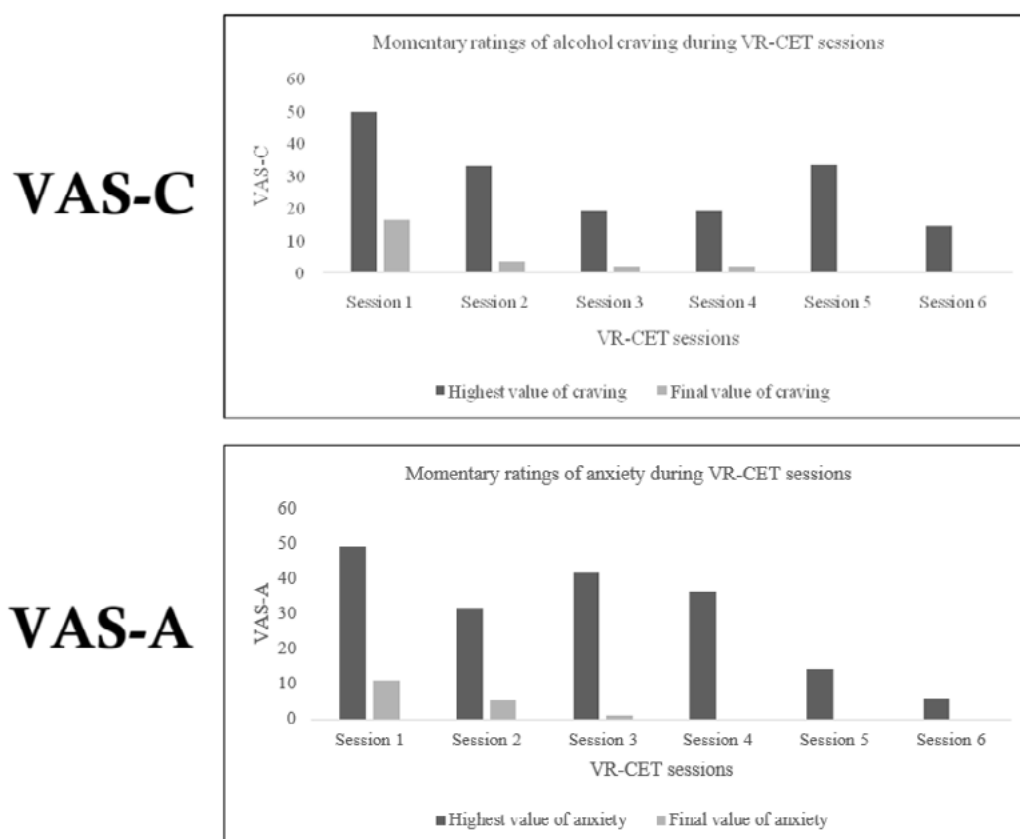


Figure 5
Momentary levels of alcohol craving reported on VAS-C and VAS-A

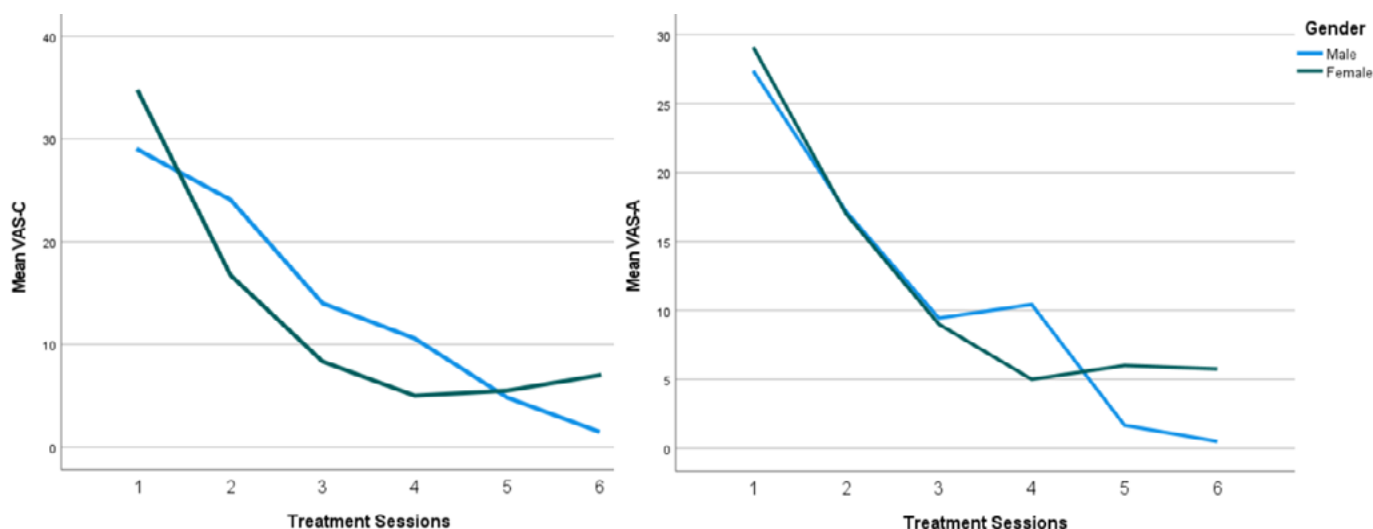


Table 4
Relapses at follow-up and comparison through Chi-square tests

	Total	EG	CG	p-value
3 months (n=43)	14/43 (32.55%)	6/18 (33.34%)	8/25 (32.00%)	0.998
6 months (n=19)	11/19 (57.89%)	4/7 (57.14%)	7/12 (58.33%)	0.997
12 months (n=12)	8/12 (66.67%)	3/5 (60.00%)	5/7 (71.42%)	0.992

Discussion

The study aimed to evaluate the efficacy of Virtual Reality – Cue Exposure Therapy (VR-CET) + Treatment as Usual (TAU) (experimental group -EG-) in comparison to TAU alone (control group -CG-), in terms of alcohol craving and anxiety levels; as well as to explore long-term effects of VR-CET versus TAU at follow-up timepoints (3, 6, and 12 months) after treatment completion. The clinical population consisted of patients diagnosed with AUD, who were considered resistant to TAU.

The first hypothesis yielded mixed results. The data indicated no significant treatment effects on alcohol craving (MACS, MACS-VR, and VAS-C) and anxiety (STAI-State and VAS-A). Nevertheless, the results showed significant principal effects of “time” over cue-induced craving (measured by MACS-VR) and anxiety (measured by STAI-State). There was no significant interaction between “type of treatment” and “time” regarding craving and anxiety. The “time” factor (pre-test versus post-test) had an effect on craving (MACS-VR) and anxiety (STAI-State) regardless of the type of treatment the participants received. Although the differences were not statistically significant, the VR assessment of cue-induced craving (VAS-C) and anxiety (VAS-A) reflected a tendency of the

EG to report lower scores on both VAS-C and VAS-A in all of the four VR environments; this tendency is endorsed by the effect sizes stated in the pre-post differences between both therapeutic approaches, as displayed in Table 3, figures in turn highlighted by the fact that VR contributes and provides the added value of controlling the input variables in a safe and secure context.

Hypothesis 2 was confirmed, as reflected by the analysis of momentary levels of VAS-C and VAS-A during the intra-VR-CET sessions in the experimental group (EG), which revealed a gradual decrease in alcohol craving and anxiety levels, progressing from the initial to the final session (as depicted in Figures 4 and 5). By the end of the therapy, participants reported minimal levels of both craving and anxiety. These findings underscore the effectiveness of VR-CET in mitigating cue-induced alcohol craving and anxiety within VR alcohol-related environments. Furthermore, these results align with research conducted in other mental health domains, such as post-traumatic stress disorder (Kothgassner et al., 2019) and anxiety disorders (Freeman et al., 2017).

The data corresponding to hypothesis 3 were contrary to our expectations, and no statistically significant differences

were observed between groups in terms of relapses at follow-ups. This suggests that both approaches (i.e., TAU and TAU+VR-CET) provide similar relapse-rates at medium and long term. These results should nonetheless be generalized cautiously, since the high drop-out rates, yet consistent with other studies in the field (Stohs et al., 2019), longitudinally hinder any potential conclusions in this framework.

Implications of the VR in AUD

The data from this study underscore the potential of technological advancements to offer valuable insights into the treatment-resistant patterns observed in individuals with AUD. Virtual reality technology offers a more ecologically valid approach compared to traditional cue-exposure techniques (Simon et al., 2020), and can complement and upgrade existing methods in clinical psychology in terms of treatment approaches (Segawa et al., 2020). Fully immersive VR environments, enriched with motivating sensory stimuli and enabling extensive interaction, provide a heightened sense of realism. This VR approximation to real-life scenarios can elicit momentary responses, such as cue-induced alcohol craving or anxiety. The theoretical foundation of VR-CET aligns with the core principles of systematic desensitization (Hernández-Serrano et al., 2020). This approach aims to diminish or extinguish reactions to alcohol-related cues and contexts, such as alcohol craving (Mellentin et al., 2016). Our research showed that prolonged, gradual, and systematic exposure significantly reduced responses to VR alcohol-related stimuli in patients with AUD as reflected by the intra-session data from the experimental group.

Limitations

Our study must be interpreted within the context of its limitations. Firstly, there was an imbalance in gender representation, and variables such as medication type and co-morbid psychopathological conditions were not controlled for. This was mainly due to the focus on treatment-resistant patterns in AUD, which made participant recruitment challenging. On another note, simple randomization was used for two fundamental reasons: simplicity, and absence of selection bias, as all subjects had equal probabilities of being assigned to one group or the other. Obviously, the greatest disadvantage of this method is the potential quantitative “imbalance” in the number of subjects between or across groups (as it happened, indeed, in our study), although the baseline comparison analyses of both groups guarantee an adequate and unbiased distribution of the subjects of study. Another limitation of the study was reflected by the overall drop-out rates. A total of 85 AUD patients were initially recruited for this study, with 51 successfully completing the protocol. It is worth noting that high non-adherence rates are commonplace in

this field, primarily due to the elevated levels of alcohol craving experienced during AUD treatment, which often lead to relapses both during and after treatment (Stohs et al., 2019). Additionally, the severity of AUD among our patients was considerable, as they all exhibited treatment-resistant patterns, representing the most severe end of the AUD spectrum. This underscores the significant challenges involved in managing recovery (Slidrecht et al., 2019), especially among our participants who were also diagnosed with co-morbid disorders such as anxiety, depression, or personality disorders. These co-occurring conditions further complicated communication and data collection processes. The results stemming specifically from hypothesis 2 should be cautiously generalized, since the authors did not compare the results of the EG vs CG, a fact that hinders and limits the statement on the relative effectiveness of both treatments. Finally, another significant limitation of the study refers to the follow-up data collection process itself. In substance use disorder research, variables such as time to/until lapse and relapse, total alcohol consumption, (heavy) drinking days, standard drink units per day, abstinence time, or craving (Bogenschutz et al., 2022; Brecht & Herbeck, 2014; Carroll et al., 2014; Slidrecht et al., 2019) are reported as indicators of treatment outcomes as part of the long-term data (at follow-ups) derived from clinical trials. Although our initial plan was to also consider several of these indicators, the COVID-19 pandemic led to collecting data from the patients at follow-up time points through phone calls instead of attending the Addictive Behaviors Unit in person. This critically interfered with reaching patients, in addition to patients having difficulties to accurately recall information about their alcohol use. Based on the limited data collected from the patients, we followed a previous study (Andersson et al., 2019), and we created a dichotomous item regarding alcohol use (yes/no) as a measure of treatment outcomes at 3-, 6-, and 12-month follow-ups (Table 4).

Future research directions

VR has shown promising short-term results, however further longitudinal research is necessary to assess the long-term effects of VR-CET on individuals with AUD (Durl et al., 2017). We acknowledge the importance of conducting an initial RCT with VR-CET in treatment-resistant adults with AUD, but we also suggest exploring additional complementary interventions (e.g., coping skills training) to potentially enhance treatment outcomes. Also, we strongly recommend incorporating measures to investigate the generalization of therapy effects to the everyday lives of patients to mitigate potential learning effects. Finally, further studies should include complementary measures, such as patients' perceived acceptability, a fact that will endorse and enhance the information on the usability and feasibility of the therapy itself.

Conclusions

The “time” factor (pre-test versus post-test) had an effect on craving and anxiety regardless of the type of treatment (EG vs CG) the participants received. Data from VR assessment indicated a tendency of the EG to report lower scores on both anxiety and craving in all of the four VR environments, a fact that is endorsed and supported by the differences in the effect sizes calculated between both treatment groups across the four environments. Additionally, participants in the EG displayed a gradual intra-session reduction in momentary alcohol craving and anxiety levels, from the first to the last session. In terms of relapse at follow-ups, the results should be interpreted cautiously since the limited data collection interferes with drawing solid conclusions about the long-term effects of VR-CET. More longitudinal research is therefore needed.

Although the incorporation of VR-CET into TAU programs may offer significant benefits, particularly in addressing alcohol craving and anxiety, the results of the present study should be interpreted carefully: 1) Future studies should expand their focus to include additional outcomes, such as total alcohol consumption, time to/ until lapse and relapse, (heavy) drinking days, standard drink units per day, abstinence time, or craving, to provide a more comprehensive understanding of the potential contributions of VR-CET in recovery management; 2) More long-term empirical research is warranted utilizing VR-CET in patients with AUD with different severity symptoms (mild, moderate, severe); 3) Further psychometric evaluation of VR should be conducted to compare traditional paper-and-pencil questionnaires with VR assessment.

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Conflicts of Interest

The authors declare no conflicts of interest.

References

- American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders (5th ed): DSM-5*. Arlington, VA: American Psychiatric Association.
- Andersson, H. W., Wenaas, M. & Nordfjærn, T. (2019). Relapse after inpatient substance use treatment: A prospective cohort study among users of illicit substances. *Addictive Behaviors*, 90, 222–228. <https://doi.org/10.1016/j.addbeh.2018.11.008>
- Anker, J. J., Kummerfeld, E., Rix, A., Burwell, S. J. & Kushner, M. G. (2018). Causal Network Modeling of the determinants of drinking behavior in comorbid alcohol use and anxiety disorder. *Alcoholism, Clinical and Experimental Research*, 43, 91–97. <https://doi.org/10.1111/acer.13914>
- Association, W. M. (2001). World Medical Association Declaration of Helsinki: Ethical principles for medical research involving human subjects. *Bulletin of the World Health Organization*, 79(4), 373–374. <https://doi.org/10.1111/ddg.13528>
- Babor, T. F., Biddle-Higgins, J. C., Saunders, J. B. & Monteiro, M. G. (2001). *AUDIT: The Alcohol Use Disorders Identification Test: Guidelines for Use in Primary Health Care*. Geneva, Switzerland: World Health Organization. <https://iris.who.int/handle/10665/67205>
- Bados, A., Gómez-Benito, J. & Balaguera, G. (2010). The State-Trait Anxiety Inventory, Trait Version: Does it really measure anxiety? *Journal of Personality Assessment*, 92, 560–567
- Bakker, M., van Dijk, A. & Wicherts, J. M. (2012). The Rules of the Game Called Psychological Science. *Perspectives on Psychological Science*, 7(6), 543–554. <https://doi.org/10.1177/1745691612459060>
- Bernard, L., Cyr, L., Bonnet-Suard, A., Cutarella, C. & Bréjard, V. (2021). Drawing alcohol craving process: A systematic review of its association with thoughtsuppression, inhibition and impulsivity. *Heliyon*, 7, e05868. <https://doi.org/10.1016/j.heliyon.2020.e05868>
- Bogenschutz, M. P., Ross, S., Bhatt, S., Baron, T., Forcehimes, A. A., Laska, E., Mennenga, S. E., O'Donnell, K., Owens, L. T., Podrebarac, S., Rotrosen, J., Tonigan, J. S. & Worth, L. (2022). Percentage of heavy drinking days following Psilocybin-Assisted Psychotherapy vs Placebo in the treatment of adult patients with Alcohol Use Disorder: A randomized clinical trial. *JAMA Psychiatry*, 79(10), 953–962. <https://doi.org/10.1001/jamapsychiatry.2022.2096>
- Brecht, M. L. & Herbeck, D. (2014). Time to relapse following treatment for methamphetamine use: A long-term perspective on patterns and predictors. *Drug and Alcohol Dependence*, 139, 18–25. <https://doi.org/10.1016/j.drugalcdep.2014.02.702>
- Byrne, S. P., Haber, P., Baillie, A., Giannopolous, V. & Morley, K. (2019). Cue exposure therapy for alcohol use disorders: What can be learned from exposure therapy for anxiety disorders?. *Substance use & misuse*, 54(12), 2053–2063. <https://doi.org/10.1080/10826084.2019.1618328>
- Carroll, K. M., Kiluk, B. D., Nich, C., DeVito, E. E., Decker, S., LaPaglia, D., Duffey, D., Babuscio, T. A. &

- Ball, S. A. (2014). Toward empirical identification of a clinically meaningful indicator of treatment outcome: Features of candidate indicators and evaluation of sensitivity to treatment effects and relationship to one year follow up cocaine use outcomes. *Drug and Alcohol Dependence*, 137, 3–19. <https://doi.org/10.1016/j.drugalcdep.2014.01.012>
- Cohen, L., Manion, L. & Morrison, K. (2007). Research methods in education (6th Ed.). New York, NY: Routledge.
- Conklin, C. A. & Tiffany, S. T. (2002). Applying extinction research and theory to cue-exposure addiction treatments. *Addiction (Abingdon, England)*, 97(2), 155–167. <https://doi.org/10.1046/j.1360-0443.2002.00014.x>
- Contel, M., Gual, A. & Colom, J. (1999). Test para la identificación de trastornos por uso de alcohol (AUDIT): Traducción y validación del AUDIT al catalán y castellano. *Adicciones*, 11(4), 337–347.
- Donovan, D. M., Kivlahan, D. R., Doyle, S. R., Longabaugh, R. & Greenfield, S. F. (2006). Concurrent validity of the Alcohol Use Disorders Identification Test (AUDIT) and AUDIT zones in defining levels of severity among out-patients with alcohol dependence in the COMBINE study. *Addiction*, 101(12), 1696–1704.
- Drummond, D. C. (2001). Theories of drugs craving, ancient and modern. *Addiction*, 96, 33–46. <https://doi.org/10.1080/09652140020016941>
- Durl, J., Dietrich, T., Pang, B., Potter, L. E. & Carter, L. (2017). Utilising virtual reality in alcohol studies: A systematic review. *Health Education Journal*, 77(2), 212–225. <https://doi.org/10.1177/0017896917743534>
- Faul, F., Erdfelder, E., Lang, G. A. & Buchner, A. (2007). G*Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical. *Behavior Research Methods*, 39(2), 175–191.
- Ferrer-García, M., Gutiérrez-Maldonado, J., Pla-sanjuanelo, J., Vilalta-abella, F., Riva, G., Clerici, M., Ribas-Sabate, J., Andreu-García, A., Fernandez-Aranda, F., Forcano, L., Riesco, N., Sanchez, I., Escadon-Nagel, N., Gomez-Tricio, O., Tena, V. & Dakanalis, A. (2017). A randomised controlled comparison of second-level treatment approaches for treatment-resistant adults with bulimia nervosa and binge eating disorder: assessing the benefits of virtual reality cue exposure therapy. *European Eating Disorder Review*, 25(6), 479–490. <https://doi.org/10.1002/erv.2538>
- Freeman, D., Reeve, S., Robinson, A., Ehlers, A., Clark, D., Spanlang, B. & Slater, M. (2017). Virtual reality in the assessment, understanding, and treatment of mental health disorders. *Psychological Medicine*, 47(14), 2393–2400. <https://doi.org/10.1017/S003329171700040X>
- Ghiță, A. & Gutiérrez-Maldonado, J. (2018). Applications of virtual reality in individuals with alcohol misuse: A systematic review. *Addictive Behaviors*, 81, 1–11. <https://doi.org/10.1016/j.addbeh.2018.01.036>
- Ghiță, A., Hernández-Serrano, O., Fernández-Ruiz, Y., Monras, M., Ortega, L., Mondon, S., Teixidor, L., Gual, A., Porras-García, B., Ferrer-García, M. & Gutiérrez-Maldonado, J. (2019b). Cue-elicited anxiety and alcohol craving as indicators of the validity of ALCO-VR software: A Virtual Reality study. *Journal of Clinical Medicine*, 8(8), 1153–1168. <https://doi.org/10.3390/jcm8081153>
- Ghiță, A., Teixidor, L., Monras, M., Ortega, L., Mondon, S., Gual, A., Paredes, S. M., Villares Urgell, L., Porras-García, B., Ferrer-García, M. & Gutiérrez-Maldonado, J. (2019a). Identifying triggers of alcohol craving to develop effective virtual environments for cue exposure therapy. *Frontiers in Psychology*, 10, 1–11. <https://doi.org/10.3389/fpsyg.2019.00074>
- Guardia-Serecigni, J., Luquero, E., Siñol, N., Burguete, T. & Cardús, M. (2006). Utilidad de la Escala Multidimensional de Craving de Alcohol (EMCA) en la práctica clínica. *Adicciones*, 18, 265–273.
- Guardia-Serecigni, J., Segura, L., Gonzalvo, B., Trujols, J., Tejero, A., Suárez, A. & Martí, A. (2004). Estudio de validación de la Escala Multidimensional de Craving de Alcohol. *Medicina Clínica*, 123(6), 211–216. <https://doi.org/10.1157/13064414>
- Guillén-Riquelme, A. & Buela-Casal, G. (2011). Psychometric revision and differential item functioning in the State Trait Anxiety Inventory (STAI). *Psicothema*, 23(3), 510–515. <https://doi.org/10.5260/chara.14.1.16>
- Hedeker, D. & Gibbons, R.D. (2006). Longitudinal Data Analysis. John Wiley & Sons, New Jersey.
- Hernández-Serrano, O., Ghiță, A., Fernández-Ruiz, J., Monras, M., Gual, A., Gacto, M., Porras-García, B., Ferrer-García, M. & Gutiérrez-Maldonado, J. (2021). Determinants of Cue-Elicited Alcohol Craving and Perceived Realism in Virtual Reality Environments among Patients with Alcohol Use Disorder. *Journal of Clinical Medicine*, 10(11), 2241. <http://dx.doi.org/10.3390/jcm10112241>
- Hernández-Serrano, O., Ghiță, A., Figueras-Puigdemralls, N., Fernández-Ruiz, J., Monras, M., Ortega, L., Mondon, S., Teixidor, L., Gual, A., Ugas-Ballester, L., Fernández, M., Montserrat, R., Porras-García, B., Ferrer-García, M. & Gutiérrez-Maldonado, J. (2020). Predictors of changes in alcohol craving levels during a Virtual Reality Cue Exposure Treatment among patients with alcohol use disorder. *Journal of Clinical Medicine*, 9(9), 3018-undefined. <https://doi.org/10.3390/jcm9093018>
- Hone-Blanchet, A., Wensing, T. & Fecteau, S. (2014). The use of virtual reality in craving assessment and cue-exposure therapy in substance use disorders. *Frontiers in Human Neuroscience*, 8(844), 1–15. <https://doi.org/10.3389/fnhum.2014.00844>

- Kang, M., Ragan, B. G. & Park, J. H. (2008). Issues in outcomes research: an overview of randomization techniques for clinical trials. *Journal of athletic training*, 43(2), 215–221. <https://doi.org/10.4085/1062-6050-43.2.215>
- Kiyak, C., Simonetti, M. E., Norton, S. & Deluca, P. (2023). The efficacy of cue exposure therapy on alcohol use disorders: A quantitative meta-analysis and systematic review. *Addictive behaviors*, 139, 107578. <https://doi.org/10.1016/j.addbeh.2022.107578>
- Kothgassner, O. D., Goreis, A., Kafka, J. X., Van Eickels, R. L., Plener, P. L. & Felnhofer, A. (2019). Virtual reality exposure therapy for posttraumatic stress disorder (PTSD): A meta-analysis. In *European Journal of Psychotraumatology* (Vol. 10, Issue 1, pp. 1654782-undefined). Taylor and Francis Ltd. <https://doi.org/10.1080/20008198.2019.1654782>
- Kranzler, H. R. & Soyka, M. (2018). Diagnosis and pharmacotherapy of alcohol use disorder: A review. *Journal of the American Medical Association*, 320(8), 815–824. <https://doi.org/10.1001/jama.2018.11406>
- Kuntsche, E., Kuntsche, S., Thrul, J. & Gmel, G. (2017). Binge drinking: Health impact, prevalence, correlates and interventions. *Psychology and Health*, 32(8), 976–1017. <https://doi.org/10.1080/08870446.2017.1325889>
- Malbos, E., Borwell, B., Einigscain, M., Korchia, T., Cantalupi, R., Boyer, L. & Lancon, C. (2023). Virtual reality cue exposure therapy for tobacco relapse prevention: A comparative study with standard intervention. *Psychological Medicine*, 53, 5070–5080. <https://doi.org/10.1017/S0033291722002070>
- Manchery, L., Yarmush, D. E., Luehring-Jones, P. & Erbllich, J. (2017). Attentional bias to alcohol stimuli predicts elevated cue-induced craving in young adult social drinkers. *Addictive Behaviors*, 70, 14–17. <https://doi.org/10.1016/j.addbeh.2017.01.035>
- Mann, K. & Hermann, D. (2010). Individualised treatment in alcohol-dependent patients. *European Archives of Psychiatry and Clinical Neuroscience*, 260, 116–120. <https://doi.org/10.1007/s00406-010-0153-7>
- McCaul, M. E., Hutton, H. E., Stephens, M. A. C., Xu, X. & Wand, G. S. (2017). Anxiety, anxiety sensitivity, and perceived stress as predictors of recent drinking, alcohol craving, and social stress response in heavy drinkers. *Alcoholism: Clinical and Experimental Research*, 41(4), 836–845. <https://doi.org/10.1111/acer.13350>
- McCormick, E. (2021). Multi-Level Multi-Growth Models: New opportunities for addressing developmental theory using advanced longitudinal designs with planned missingness. *Developmental Cognitive Neuroscience*, 51, 101001. <https://doi.org/10.1016/j.dcn.2021.101001>
- Mellentin, A. I., Nielsen, B., Nielsen, A. S., Yu, F. & Stenager, E. (2016). A randomized controlled study of exposure therapy as aftercare for alcohol use disorder: study protocol. *BMC Psychiatry*, 16, 112–120. <https://doi.org/10.1186/s12888-016-0795-8>
- Mellentin, A. I., Skøt, L., Nielsen, B., Schippers, G. M., Nielsen, A. S., Stenager, E. & Juhl, C. (2017). Cue exposure therapy for the treatment of alcohol use disorders: A meta-analytic review. *Clinical Psychology Review*, 57, 195–207. <https://doi.org/10.1016/j.cpr.2017.07.006>
- Morean, M. E., L'Insalata, A., Butler, E. R., McKee, A. & Krishnan-Sarin, S. (2018). Age at drinking onset, age at first intoxication, and delay to first intoxication: Assessing the concurrent validity of measures of drinking initiation with alcohol use and related problems. *Addictive Behaviors*, 79, 195–200. <https://doi.org/10.1016/j.addbeh.2017.12.017>
- Mystakidou, K., Tsilika, E., Parpa, E., Sakkas, P. & Vlahos, L. (2009). The psychometric properties of the Greek version of the State-Trait Anxiety Inventory in cancer patients receiving palliative care. *Psychology and Health*, 24, 1215–1228.
- Naqvi, N. H. & Morgenstern, J. (2015). Cognitive Neuroscience Approaches to Understanding Behavior Change in Alcohol Use Disorder Treatments. *Alcohol research : current reviews*, 37(1), 29–38.
- Parsons, T. D. (2015). Virtual Reality for Enhanced Ecological Validity and Experimental Control in the Clinical, Affective and Social Neurosciences. *Frontiers in human neuroscience*, 9, 660. <https://doi.org/10.3389/fnhum.2015.00660>
- Patterson Silver Wolf, D. A., BlackDeer, A. A., Beeler-Stinn, S., Zheng, K. & Stazrad, K. (2021). Performance-based practice: Clinical dashboards for addiction treatment retention. *Research on Social Work Practice*, 31(2), 205–211. doi:<https://doi.org/10.1177/1049731520972798>
- Patterson Silver Wolf, D., Dulmus, C. N., Maguin, E., Linn, B. K. & Hales, T. W. (2019). Therapist–patient demographic profile matching: A movement toward performance-based practice. *Research on Social Work Practice*, 29(6), 677–683. doi:<https://doi.org/10.1177/1049731518783582>
- Patterson Silver Wolf, D. A., Dulmus, C. N., Wilding, G. E., Yu, J., Barczykowski, A. L., Shi, T., Diebold, J. R., Harvey, S. J., Tomasello, N. M. & Linn, B. K. (2022). Treatment resistant alcohol use disorder. *Alcoholism Treatment Quarterly*, 40(2), 205–216. <https://doi.org/10.1080/07347324.2021.1989994>
- Segawa, T., Baudry, T., Bourla, A., Blanc, J. V., Peretti, C. S., Mouchabac, S. & Ferreri, F. (2020). Virtual Reality (VR) in assessment and treatment of addictive disorders: A systematic review. *Frontiers in Neuroscience*, 13, 1–14. <https://doi.org/10.3389/fnins.2019.01409>
- Simon, J., Etienne, A. M., Bouchard, S. & Quertemont, E. (2020). Alcohol Craving in Heavy and Occasional Alcohol Drinkers After Cue Exposure in a Virtual Environment: The Role of the Sense of Presence. *Frontiers*

- in *human neuroscience*, 14, 124. <https://doi.org/10.3389/fnhum.2020.00124>
- Sliedrecht, W., de Waart, R., Witkiewitz, K. & Roozen, H. G. (2019). Alcohol use disorder relapse factors: A systematic review. *Psychiatry Research*, 278, 97–115. <https://doi.org/10.1016/j.psychres.2019.05.038>
- Spielberger, C. D., Gorsuch, R. L. & Lushene, R. (1982). *Manual del Cuestionario de Ansiedad Estado/Rasgo (STAI)*. Madrid, España: TEA Ediciones
- Steele, F. (2008). Multilevel Models for Longitudinal Data. *Journal of the Royal Statistical Society, Series A*, 171, 5–19.
- Stohs, M. E., Schneekloth, T. D., Geske, J. R., Biernacka, J. M. & Karpyak, V. M. (2019). Alcohol craving predicts relapse after residential addiction treatment. *Alcohol & Alcoholism*, 1–5. <https://doi.org/10.1093/alcalc/agy093/5363992>
- Sullivan, G. M. & Feinn, R. (2012). Using Effect Size-or Why the P Value Is Not Enough. *Journal of graduate medical education*, 4(3), 279–282. <https://doi.org/10.4300/JGME-D-12-00156.1>
- Suresh, K. (2011). An overview of randomization techniques: An unbiased assessment of outcome in clinical research. *Journal of Human Reproductive Sciences*, 4, 8–11. <https://doi.org/10.4103/0974-1208.82352>
- Trahan, M. H., Maynard, B. R., Smith, K. S., Farina, A. S. J. & Khoo, Y. M. (2019). Virtual Reality Exposure Therapy on Alcohol and Nicotine: A Systematic Review. *Research on Social Work Practice*, 29(8), 876–891. <https://doi.org/10.1177/1049731518823073>
- Witkiewitz, K., Litten, R. Z. & Leggio, L. (2019). Advances in the science and treatment of alcohol use disorder. *Science Advances*, 5(9), eaax4043. <https://doi.org/10.1126/sciadv.aax4043>
- Witkiewitz, K., Roos, C. R., Pearson, M. R., Hallgren, K. A., Maisto, S. A., Kirouac, M., Forcehimes, A. A., Wilson, A. D., Robinson, C. S., McCallion, E., Tonigan, J. S. & Heather, N. (2017). How much is too much? Patterns of drinking during alcohol treatment and associations with post-treatment outcomes across three alcohol clinical trials. *Journal of Studies on Alcohol and Drugs*, 78, 59–69. <https://doi.org/10.15288/jsad.2017.78.59>

