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Cognitive-behavioral treatment and antidepressants combined with virtual reality exposure for patients with chronic agoraphobia

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Abstract In this study we compared the efficacy of virtual reality exposure combined with cognitive-behavioral therapy (VRET) to that of traditional cognitive-behavioral therapy (CBT) alone in reducing phobic symptoms in a sample of patients with long-term agoraphobia. The study was a between-subject design with three experimental conditions (VRET group, $N = 30$; CBT group, $N = 30$; and medication only group, $N = 20$) and repeated measures (pre-treatment, post-treatment, and six-month follow-up). All patients were receiving antidepressant medication. Results showed that all therapies were statistically effective both at post-treatment and six-month follow-up. The VRET group showed clinical improvement in most variables measured at follow-up. The CBT group showed the highest dropout rates. These results are discussed pointing out that VRET probably serves as an intermediate procedure for an efficient exposure to phobic stimuli. Besides describing the advantages of VRET for the treatment of agoraphobia symptoms in cost-benefit terms, the study also considered issues related to higher treatment adherence and motivation.

PALABRAS CLAVE
Agorafobia;
Realidad virtual;
Terapia cognitivo-conductual;

Resumen En este estudio se comparó la eficacia de la exposición a estímulos virtuales combinada con terapia cognitivo-conductual (VRET) con un programa tradicional cognitivo-conductual (CBT) para reducir la sintomatología fóbica en una muestra de personas con agorafobia de larga evolución. Se utilizó un diseño entre sujetos con tres condiciones experimentales (grupo VRET, $N = 30$; grupo CBT, $N = 30$; y grupo con sólo medicación, $N = 20$) y medidas repetidas (pre, post-

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Estudio experimental

tratamiento y seguimiento a los seis meses). Todos los pacientes estaban tomando antidepresivos. Los resultados mostraron que todas las terapias fueron estadísticamente eficaces, tanto en el post-tratamiento como en el seguimiento. El grupo VRET mostró mayores mejoras clínicas en el seguimiento. El grupo CBT mostró las tasas más altas de abandono. VRET probablemente juega un papel intermedio para una exposición eficiente a los estímulos fóbicos. Más allá de las ventajas de un procedimiento VRET para el tratamiento de la agorafobia en términos de coste-beneficios, este estudio también destaca los posibles beneficios en la mejora en la motivación y adherencia al tratamiento.

Anxiety disorders are a clinical problem that affects a considerable sector of the population. According to several epidemiological studies conducted according to the WHO criteria (e.g., ESEMeD, 2004, in six European countries), these disorders have a lifetime and past-year prevalence of about 15% and 6%, respectively. Anxiety disorders affect mostly women, who represent about 75% of patients. One of these disorders is agoraphobia, the most complex and disabling phobia in the phobia spectrum.

Today, effective therapeutic resources are available for the treatment of agoraphobia. Among psychiatric drugs, a number of antidepressant medications have shown efficacy regarding symptom remission. Specifically, paroxetine and venlafaxine have proven to be highly effective and tolerable by patients (Farach et al., 2012; Mochcovitch & Nardi, 2010). Cognitive-behavioral therapy (CBT) is available as a psychological treatment package for agoraphobia. The efficacy of CBT can increase when gradual exposure to phobic stimuli is included in the program (Baker, Patterson, & Barlow, 2002; Culver, Stoyanova, & Craske, 2012).

There are different types of exposure. In vivo exposure therapy seems to be the most effective type (Wiederhold & Rizzo, 2005). However, many patients are reluctant to confront real stimuli. In this regard, virtual reality (VR) stimuli can play an intermediate role; instead of being directly confronted with real stimuli, patients are confronted with their virtual counterpart (Shiban, Pauli, & Mühlberger, 2013). Virtual reality exposure treatment (VRET) is a procedure that is similar to CBT but uses VR (usually combined with in vivo stimuli) to expose patients to feared stimuli. Both traditional CBT exposure and VRET are based on the model of emotional processing of fear (Abramowitz, Deacon, & Whiteside, 2011; Foa, Huppert, & Cahill, 2006; Neudeck & Wittchen, 2012; Reinecke, Rinck, Becker, & Hoyer, 2013), although the underlying processes still remain controversial (e.g., Kämpfe et al., 2012).

Several reviews about anxiety treatment (i.e., de Carvalho, Freire, & Nardi, 2010; Krijn, Emmelkamp, Olafsson, & Biemond, 2004; Opriş et al., 2012; Peñate, 2012; Powers & Emmelkamp, 2008) have shown that VRET appears to be more effective than in-imagination exposure; in fact, VRET seems to yield similar results to in vivo exposure as long as the 'sensation of presence' (i.e., the feeling of being inside the virtual environment) is guaranteed (Alsina-Jurnet, Gutiérrez-Maldonado, & Rangel-Gómez, 2011). Specific data on agoraphobia are less conclusive: Meyerbroeker, Morina, Kerkhof, and Emmelkamp (2013) found that traditional CBT with in vivo exposure led to better results than VRET. Yet, Botella et al. (2007), Gonzalez-Lorenzo et al. (2011), and Pitti et al. (2008) found that VRET was able to yield similar (or better) results than CBT, especially when combined with in vivo exposure. This combination was found to obtain better results than VRET alone (Malbos, Rapee, & Kavakli, 2013).

As pointed out by de Carvalho et al. (2010), VRET has some advantages because it overcomes some limitations of in vivo techniques. This is especially true with long-term agoraphobia. Patients with chronic agoraphobia tend to have high dropout rates, be reluctant to new exposure, and overuse benzodiazepines. They often have a history of unsuccessful in vivo exposure and experience panic attacks and therefore do not adhere to new exposure treatment or drop out during its application. VRET can appear as an attractive and safe resource for such patients. VR stimuli can play an intermediate role, increase confidence in the technique and patient compliance, and reduce dropout rates.

In the context of cognitive-behavioral therapies, the aim of this study was to assess the efficacy of VRET in multiple context exposure (Balooch & Neumann, 2011; Shiban et al., 2013) combined with in vivo exposure as a therapeutic program to improve treatment compliance and reduce dropout rates in patients with long-term agoraphobia (i.e., more than 5 years of evolution of the disorder). We intended to compare the efficacy of the above-mentioned treatment with that of traditional exposure therapy (CBT), and antidepressants alone.

It should be noted that long-term agoraphobia patients are medicated (or self-medicated) with a number of different psychodrugs. They are resistant to discontinue medication because they consider it necessary to prevent anxiety attacks. To control the role of psychodrugs in the final results and increase sample homogeneity, researchers ensured that patients used the same group of antidepressants (i.e., paroxetine and venlafaxine) as the most efficient drugs to control agoraphobia symptoms (i.e., Farach et al., 2012).

Our main hypothesis was that combined VRET + in vivo exposure would lead to similar statistical and clinical improvements as traditional exposure therapy (CBT) and better results than medication alone, but VRET would achieve better treatment compliance and lower dropout rates.

Method

Participants

Patients were referred from mental health units of the Psychiatric Service of the Canary Islands University Hospital, in Spain, where the study was conducted from September 2011 to July 2012. Inclusion criteria for participants were meeting the criteria of the DSM-IV-TR (American Psychiatric Association [APA], 2000) and ICD-10 (World Health Organization [WHO], 1992) for the diagnosis of agoraphobia (with or without panic disorder). Exclusion criteria were having a diagnosis of psychosis, personality disorders, or other anxiety disorders with agoraphobia disorder as a secondary diagnosis. All participants signed a consent form approved by the institutional ethics committee of the Canary Islands University Hospital. Once admitted, patients were assigned to three treatment groups according to a previously generated table of random numbers, indicating which numbers belonged to each group.

From an initial sample of 80 patients, 50 patients with five or more years of evolution of agoraphobia (with and without panic attacks) completed the entire treatment phase. Dropout rates are described in the Results section. Intention-to-treat analyses were conducted using the last-observation-carried-forward method.

Of the the 50 participants who completed the treatment, 11 had been diagnosed with agoraphobia without panic disorder and 39 had been diagnosed with agoraphobia with panic disorder. The age range was 24 to 60 years. Most participants in the sample were women (72%). Regarding marital status, 48%were married, 40%were single, and 12% were separated or divorced. Evolution time of clinical symptoms ranged from 5 to 30 years, with a mean evolution time of 11.46 years (SD = 6.1).

A single therapist applied both CBT in vivo exposure treatment and VRET. The therapist was a clinical psychologist with more than 15 years' experience as a practitioner.

Material and apparatus

The following measuring instruments were administered to assess and verify the diagnosis of agoraphobia:

- Composite International Diagnostic Interview (CIDI), 2.1. It is a structured interview designed to assess mental disorders according to the criteria established by the ICD-10 (Kessler & Üstün, 2004; WHO, 1992). Only the questions about phobias and panic were used.
- Agoraphobia Inventory (AI). The AI (Echeburúa, Corral, García, Páez, & Borda, 1992) measures general level of agoraphobia using 69 items structured into two sections. The first part measures different types of altered responses of patients alone and in company when faced with the most common stimuli associated to agoraphobic situations. The second part examines response variations as a function of factors that contribute to increasing and decreasing anxiety. For the purposes of this study, it was interesting to obtain separate scores for patients' responses when alone and in company, as two subscales (AI-accompanied and AI-alone). The authors (Echeburúa et al., 1992) describe appropriate psychometric properties for agoraphobia severity and for the selection of target behaviors in agoraphobia disorders.

The following questionnaires and scales were administered to measure clinical symptoms and therapeutic progress (outcome measures):

- Agoraphobic Cognition Questionnaire (ACQ). The ACQ (Chambless, Caputo, Bright, & Gallagher, 1984) assesses catastrophic thoughts that occur when experiencing anxiety on a 5-point Likert scale. The authors have reported a final adequate internal consistency (α = .80), high test-retest stability (r = .86), and final one-factor solution. Also, the total score discriminates between patients with agoraphobia and a normal control sample.
- Body Sensations Questionnaire (BSQ). The BSQ (Chambless et al., 1984) is a self-report questionnaire composed of 17 items about physical sensations when experiencing anxiety, rated on a 5-point Likert scale. Again, the authors have reported high internal consistency (α = .87), moderate test-retest stability (r = .67), and the scale discriminate between patients with agoraphobia and a normal control sample.
- Beck Anxiety Inventory (BAI). The BAI (Beck, Epstein, Brown, & Steer, 1988) is a self-report instrument that measures the severity of anxiety in adults and adolescents using 21 multiple-choice items. Responses are provided on a 4-point scale. Beck et al. (1988) reported high internal consistency (α = .92), an adequate one-week test-retest stability (r = .75), and discriminant validity in describing different anxiety levels.
- Liebowitz Social Anxiety Scale (LSAS). The LSAS (Liebowitz, 1987) is a Likert scale designed to assess the severity of social anxiety disorder. The scale is composed of 24 items assessed from two approaches: 1) fear experienced by the patient in such situations (LSAS-fear), and 2) degree of avoidance of them (LSAS-avoidance). Scales have obtained high α coefficients (.92 for LSAS-fear; .92 for LSAS-avoidance; and .96 for total score), and adequate treatment sensitivity, with the following effect sizes: .65 for LSAS-fear; .67 for LSAS-avoidance; and .67 for total score (Heimberg et al., 1999).
- 0±58 to 0±67 Subjective Units of Anxiety (SUA). With this instrument, patients rate their degree of anxiety regarding phobic stimuli from 0 to 10. These measures were taken at the end of all sessions.
- Behavioral Avoidance Test (BAT). At the end of the program, patients were encouraged to cope with two real scenarios that were similar to the virtual environments. Patients were accompanied by a therapist helper. The task involved walking in those environments for a maximum of 20 minutes. Patients were informed that if they felt anxious they could return to the place where the helper was waiting and that they could also refuse to perform the task. Time (i.e., minutes on the street) and SUA measures were taken.

The Virtual Reality System and the software used in this study were the same as those used in the study by Peñate, Pitti, Bethencourt, de la Fuente, and Gracia (2008). The virtual environments were seven possible

phobic stimuli for agoraphobia patients: an airport building and a plane, a square and a street, an elevator and an underground car park, a bank office, a highway, a beach, and a cableway.

Design

A randomized clinical trial was designed. As pointed out in the Participants section, patients were selected by their psychiatrist or psychologist (i.e., non-random selection). Next, they were randomly assigned to one of the three groups according to a previous random number assignation. Based on the independent variables, we used a factorial between-subject experimental design with repeated measures (Montero & León, 2007). The design included two independent variables and one covariate (drug). The first independent variable was type of treatment (three levels). The second independent variable was time lapse between the different measuring times (three levels). Thus, the design considered three types of treatment (between-subject factor): CBT + drug, hereinafter referred to as CBT (initial *N* = 30; 23 paroxetine, 7 venlafaxine); VR + CBT + drug, hereinafter VRET (initial *N* = 30; 20 paroxetine, 10 venlafaxine); and a group of patients on the waiting list for psychological treatment + drug, hereinafter DRUG (initial *N* = 20; 15 paroxetine, 5 venlafaxine). In the CBT and VRET groups, measures (within-subject factor) were taken at three levels: pre-treatment, post-treatment, and 6-month follow-up. In the DRUG group, measures were taken at pre-treatment and post-treatment. At the end of this stage, free psychological treatment was provided to those who requested it. This group included only 20 patients (instead of 30 as in the other two groups) because the aim was just to have enough participants for statistical tests, considering, as previous studies had revealed, that this group would show the least improvement.

The following measures were used as dependent variables: cognitive and overt behaviors related to agoraphobia when the patient was alone (AI-alone) and when the patient was accompanied (AI-accompanied), agoraphobic cognitions (ACQ), physiological reactivity (BSQ), general anxiety (BAI), social anxiety: fear of situations (LSAS-fear) and avoidance of these social situations (LSAS-avoidance), and self-perceived anxiety (SUA).

Procedure

After an initial screening, a clinical psychologist confirmed the diagnosis with the CIDI 2.1 interview and the AI. Patients who accepted to participate gave written informed consent and completed the pre-treatment measures. All patients had a clinical course of at least 5 years with a diagnosis of agoraphobia disorder. All participants were taking psychodrugs (paroxetine or venlafaxine) and received a dose between 20 and 30 mg/day or between 37.5 and 75 mg/day, respectively, according to psychiatric prescription.[1] They were randomly assigned to the different combination therapy groups (CBT or VRET) or to the DRUG group.

Each experimental group received 11 individual clinical sessions that lasted 30-45 minutes each. The first three sessions were similar in both treatment groups. They consisted of a psycho-educational session and two training sessions in cognitive restructuring. Patients in the CBT group were encouraged to confront phobic environments with in vivo exposure. Patients in the VRET group received a combination of in vivo exposure and VR exposure sessions. They were exposed to the four virtual environments that had caused most anxiety in them. Subjective Units of Anxiety (SUA) measurements were taken at the end of all sessions. Once the psychotherapy sessions had ended, the post-treatment measures were taken. Six months later, patients attended a psychological and psychiatric follow-up session and completed the follow-up measures.[2]

Data analysis

Several tests were performed. First, an analysis was carried out to verify whether the dropout rate was significant in terms of group membership. Next, the three experimental groups were subjected to a pre-test/post-test repeated-measures analysis of covariance (MANCOVA) of each of the variables of the clinical symptoms, with the drug as a covariate.

Later, a pre-test, post-test, and follow-up repeated-measures MANCOVA was performed again with the two treatment groups (CBT and VRET), using type of drug (paroxetine or venlafaxine) as a covariate.

A repeated-measures analysis of variance with eight levels (seven psychotherapy sessions and one follow-up session) was conducted on the Subjective Units of Anxiety (SUA) to determine if the level of anxiety was the same at the three points in time measured and whether there was a significant interaction between the time each of the measures was taken and treatment.

Finally, an analysis was performed to distinguish the degree of acquiescence to participate in the behavioral avoidance test (BAT) for each treatment type. Another goal was to determine the level of subjective anxiety felt by patients in each of the two scenarios they were exposed to and the average exposure time.

Results

As previously anticipated, dropouts were considered first. Figure 1 represents the flowchart of the sample from pre-treatment to follow-up. As can be observed, there were considerable dropout rates. Out of the 80 patients who were assigned to different groups, 37.5% left the study during treatment; most of them (more than 50%) belonged to the CBT group. The VRET group had the lowest dropout rates. Most dropouts (*N* = 15) took place at the beginning of treatment (before the exposure sessions). The main

1. To increase the homogeneity of the sample, given that all patients were taking drugs, participants were encouraged to change their medication for the best tested medicines: paroxetine or venlafaxine. The last author, a psychiatrist, prescribed the antidepressant and its dosage according to each patient's clinical history.

2. Additional information about the program can be provided by the corresponding author.

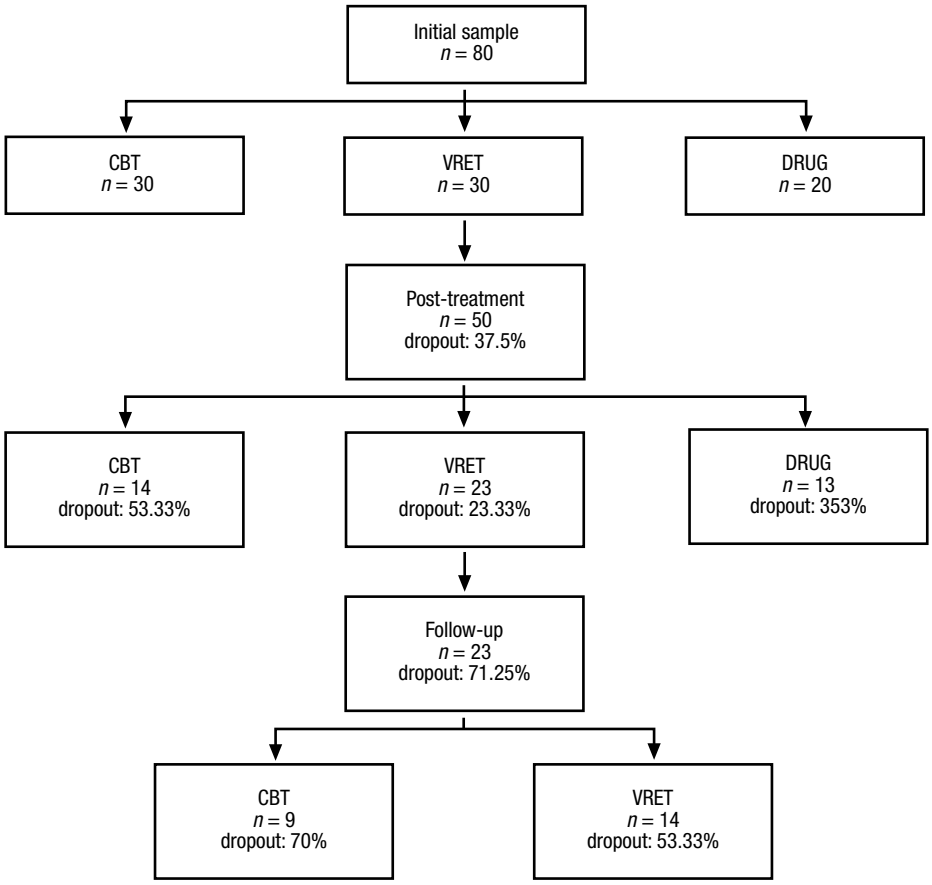

Figure 1 Flowchart representing sample assignment, sample sizes, and dropout rates (from the initial sample) at the three moments of assessment.
Note.
CBT = cognitive-behavioral treatment; VRET = virtual exposure treatment.

reasons were lack of novelty compared to previous treatments and schedule problems. Seven patients left the program when the in vivo exposure sessions began (Session 4). They considered that the task made them suffer. It was not possible to find out the reasons why another 12 patients left. A comparison with pre-treatment rates showed significant differences ($\chi^2_{(2)} = 5.83$; $p = .05$). Dropout rates increased at follow-up and, again, the group with the highest rates was the CBT group; yet, no significant differences were found at this stage ($\chi^2_{(1)} = 1.76$).

Next, a repeated-measures MANCOVA was performed with two factors: time (two levels: pre-treatment and post-treatment) and treatment (CBT, DRUG, and VRET), with drugs as a covariate. Table 1 shows the mean and standard deviation of the different conditions for each outcome measure at post-treatment and six-month follow-up. Significant differences were found in the treatment x time interaction (Wilks' Lambda = .42, $F = 1.93$, $p = .02$, $\eta^2 = .34$). Results showed a significant effect of treatment on the variable measuring agoraphobic cognitions (ACQ), $F_{(2, 41)} = 5.21$ (p = .01, $\eta^2 = .20$), body sensations (BSQ), $F_{(2, 41)} = 5.63$ (p = .00, $\eta^2 = .21$), general anxiety (BAI) $F_{(2, 41)} = 3.45$ ($p = .04$, $\eta^2 = .14$), cognitive and overt behaviors related to agoraphobia when the patient was alone (IA-alone), $F_{(2, 41)} = 5.15$ ($p = .01$, $\eta^2 = .20$), and cognitive and overt behaviors related to agoraphobia when the patient was accompanied (AI-accompanied) $F_{(2, 41)} = 4.96$ ($p = .01$, $\eta^2 = .19$). Results show that both the CBT and VRET group obtained better scores on these variables compared to the DRUG group.

Another repeated-measures MANCOVA was performed with two factors: time (three levels: pre-treatment, post-treatment, and follow-up) and treatment (CBT and VRET, because there was no follow-up of the DRUG group). No significant differences were found in the multivariate analysis. In the univariate analysis, results showed that there was only a significant effect of treatment on the variable measuring cognitive and overt behaviors related to agoraphobia when the patient was alone (IA-alone), $F_{(2, 40)} = 3.97$ ($p = .27$, $\eta^2 = .16$), where patients in the VRET group showed greater improvement.

To test the changes in Subjective Units of Anxiety (SUA), a repeated-measures analysis of variance (ANOVA) was carried out to analyze session-to-session effects. We analyzed the effects from Session 5 (when exposure was activated) to follow-up. Although the results showed a significant time effect, $F_{(4.03, 92.82)} = 3.21$, $p = .01$, $\eta 2 = .12$, the treatment x time interaction was not significant: all the treatments reduced SUA scores but no differences were found between them.

For the BAT procedure, patients were exposed to the following scenarios: "car park and elevator" (scenario 1) and "square and street" (scenario 2). Fourteen patients

Table 1 Mean and standard deviation of the outcome measures at pre-treatment, post-treatment, and follow-up.

	CBT	VRET	DRUG
	n (post-) = 14	*n* (post-) = 23	*n* (post-) = 13
	n (follow-up) = 9	*n* (follow-up) = 14	
	M (SD)	*M (SD)*	*M (SD)*
ACQ			
Pre-treatment	38.07 (9.46)	37.30 (7.63)	32.30 (9.46)
Post-treatment	25.50 (8.67)	28.72 (7.28)	30.15 (8.33)
Follow-up	28.00 (10.90)	24.57 (9.27)	
BSQ			
Pre-treatment	58.35 (9.94)	57.17 (12.79)	54.46 (11.78)
Post-treatment	39.57 (9.78)	46.27 (9.41)	50.84 (11.28)
Follow-up	45.66 (14.71)	39.07 (11.04)	
BAI			
Pre-treatment	32.57 (13.42)	30.47 (11.83)	31.38 (12.65)
Post-treatment	14.78 (9.93)	16.83 (11.52)	27.07 (13.33)
Follow-up	17.33 (8.73)	16.22 (16.64)	
AI-alone			
Pre-treatment	94.28 (47.48)	98.50 (32.39)	83.65 (33.39)
Post-treatment	69.23 (42.60)	69.23 (42.60)	96.33 (43.45)
Follow-up	77.16 (37.61)	27.92 (16.89)	
AI-accompanied			
Pre-treatment	65.07 (27.07)	70.13 (34.82)	57.15 (21.57)
Post-treatment	41.00 (38.65)	49.83 (30.19)	68.00 (26.63)
Follow-up	37.28 (21.70)	27.23 (15.54)	
LSAS-fear			
Pre-treatment	31.96 (16.52)	34.56 (19.29)	30.98 (15.77)
Post-treatment	20.76 (15.53)	28.38 (14.39)	33.33 (18.40)
Follow-up	25.71 (16.43)	16.50 (11.81)	
LSAS-avoidance			
Pre-treatment	27.59 (16.15)	31.34 (18.81)	31.31 (16.98)
Post-treatment	19.68 (16.79)	25.57 (15.34)	32.00 (20.13)
Follow-up	26.50 (16.66)	14.09 (11.49)	

Note. CBT = cognitive-behavioral treatment; VRET = virtual exposure treatment; *SD* = standard deviation; ACQ: Agoraphobic Cognition Questionnaire; BSQ = Body Sensations Questionnaire; BAI = Beck Anxiety Inventory; AI-alone = Agoraphobia Inventory ("alone" scores); AI-accompanied = Agoraphobia Inventory ("accompanied" scores); LSAS-fear = Liebowitz Social Anxiety Scale (feared stimuli); LSAS-avoidance = Liebowitz Social Anxiety Scale (avoided stimuli).

were assigned to the combination therapy groups (seven to the CBT group and seven to the VRET group). Four patients in the CBT group (and one in the VRET group) refused to take part in BAT exposure. Table 2 shows the mean time spent in each scenario and the level of perceived anxiety (SUA). It should be noted that the VRET group had lower self-perceived anxiety scores in both scenarios. According to Mann-Whitney's U coefficient, a statistical difference was found in time spent in Scenario 1 ($U = 0.00$; $p = .02$). This result showed that VRET patients spent more time than CBT patients did. No other statistical differences were found.

Overall, results failed to show statistical differences between the combination therapy groups in the outcome measures; however, the average scores on those clinical variables showed a greater decrease in some groups than others (Table 1). This differential decrease led us to consider if there were clinical differences between the experimental groups.

According to the data shown on Table 1, clinical improvement was considered to occur when the scores of variables decreased by 50% compared to pre-treatment scores (pre-treatment scores minus post-treatment scores, and pre-treatment scores minus six-month follow-up scores). Neither group showed a 50% decrease in ACQ and BSQ scores. By contrast, the VRET group showed a 50% decrease at follow-up in the rest of variables (i.e., AI-alone, AI-accompanied, LSAS-fear, LSAS-avoidance), whereas the CBT group only showed this decrease at post-treatment in general anxiety (BAI). When this analysis was performed with the group treated only with drugs, as shown on Table 1, none of the scores decreased by 50% between pre-treatment and post-treatment; instead, some scores of this group showed a slight increase at post-treatment.

Table 2 Means and sample sizes of Behavioral Avoidance Test measures.

	Scenario 1			Scenario 2		
Treatment modality	***n***	**Time mean**	**SUA mean**	***n***	**Time mean**	**SUA mean**
CBT	3	10	6	3	10	3.33
VRET	6	17.50	4.25	4	12.50	3.08

Note. SUA= Subjective Units of Anxiety; CBT = cognitive-behavioral treatment; VRET = virtual exposure treatment.

Discussion

In this study we explored the efficacy of combination therapy in a sample of patients with chronic agoraphobia (i.e., a minimum of 5 years of evolution and an average of 11.46 years with the disorder). The aim was to test the efficacy of VR techniques (i.e., a virtual system based on 7 scenarios) and compare it to traditional cognitive-behavioral treatment regarding several clinical outcome measures and dropout rates. Both psychological techniques were combined with pharmacological treatments using venlafaxine and paroxetine.

First of all, dropout rates were revealing. Results showed that 37.5% patients abandoned the program during treatment sessions, and it was especially relevant for the CBT group (more than 50%). These data are inconsistent with those reported by Opriş et al. (2012), who did not found differences in dropout rates between traditional CBT and VRET. By contrast, they are consistent with rates reported by Meyerbroeker et al. (2013) with a sample of similar severity. To explain these high rates, we must consider the nature of the sample: patients who had had agoraphobia for at least five years. Over those years, these patients may have received several psychological or psychiatric treatments with poor outcomes. Thus, we consider that it is remarkable that only seven patients out of 30 discontinued the VRET treatment, showing better adherence rates. The novelty effect and the safety of the VRET condition may have played a key role in such adherence.

According to the outcome measures, the comparison of the three groups at two points in time (pre-treatment and post-treatment) showed an improvement in different variables in the VRET and CBT groups compared to the DRUG group. Yet, when we compared the two combination therapy groups separately at the three points in time, patients treated with VR and antidepressants had lower scores than patients treated with CBT, but the VRET group showed better results in one variable. This was a relevant clinical variable, as it measured patients' ability to cope with their anxiety when they were facing the phobic stimuli alone.

Overall, results showed a better adherence in the VRET group but no statistical differences between the CBT and VRET groups. Yet, the combined effects of VRET and antidepressants showed better levels of improvement regarding clinical efficacy. This study is consistent with those of Botella et al. (2007), Gonzalez-Lorenzo et al. (2011), and Pitti et al. (2008), who obtained better results in the combination therapy group when VR techniques were used. This study also has similarities with previous ones regarding follow-up. Gonzalez-Lorenzo et al. (2011) explored six-month follow-up, Peñate et al. (2008) explored three-month follow-up, Choi et al. (2005) assessed six-month follow-up, and Botella et al. (2007) measured one-year follow-up. Again, results showed greater improvement when VR techniques were included.

Considering the greater clinical efficacy of VRET + antidepressants, we believe there are two complementary explanations. A first possible explanation may be that patients are better regulated by a process that is a good intermediate stage before confronting real phobic stimuli. VRET can play a role in the successive approximation process, facilitating the first contact with the feared stimuli. It can be an additional advantage in the treatment of long-term agoraphobia, because patients often have a history of failed in vivo exposure (Gonzalez-Lorenzo et al., 2011; Peñate et al., 2008). Another explanation is related to the mechanisms underlying VR exposure. As Meyerbröker and Emmelkamp (2010) pointed out in their review, phobic patients treated with VRET developed changes at cognitive level, increasing both the level of self-efficacy and the level of self-statements. This may imply that VR activates other mechanisms besides those proposed by the emotional processing theory (Foa et al., 2006), which may increase its efficacy compared to traditional exposure technique.

The main difference between this study and previous research is the use of a large sample of patients diagnosed with chronic agoraphobia. This study included seven local scenarios, similarly to studies performed by Botella et al. (2007), Gonzalez-Lorenzo et al. (2011), and Pitti et al. (2008), which included various virtual scenarios, although they were not all local.

It is also worth noting some limitations of this study. The most important one is its sample size. Although it was larger than in previous studies, the number of patients in each treatment group was never greater than 30. A relevant limitation is related to how results can be explained: it is not possible to explain the separate role of VRET or CBT with in vivo exposure, because the antidepressant was present. Therefore, results can only be interpreted as a function of the drug x psychological treatment interaction. Another limitation is the number of virtual scenarios. Even though the scenarios were local and therefore more realistic, the number of scenarios is likely to be insufficient, given the complexity and variability of anxiogenic situations for patients with agoraphobia.

In future research, it would be interesting to study the psychological variables that play an important role in the evaluation of virtual environments and facilitate the

activation of emotions during exposure. These combination treatments (CBT and VRET) should also be compared a larger samples to obtain results with greater statistical power. Combination therapy groups should also be compared with a group not receiving any psychopharmacological therapy. Similarly, it might be interesting to have a large number of VR exposure scenarios in the package of exposure sessions of the VR group.

In conclusion, results revealed that both combination therapy groups were statistically effective at post-treatment and six-month follow-up. However, regarding clinical efficacy, results show the following: combination therapy with VRET + antidepressants seems to be better than traditional techniques at decreasing agoraphobic cognitions, depressive symptoms, measures of anxiety, and agoraphobic cognitions and behaviors both when patients are alone and when they are accompanied, as well as social anxiety related to fear and avoidance of these situations; this combination therapy also seems better at maintaining these improvements over time. Results also demonstrate that use of antidepressants such as paroxetine (an SSRI) and venlafaxine (an SNRI) decreases symptoms of agoraphobia when combined with psychological techniques, including exposure to virtual reality, but is not as effective as treatment alone. Most important, patients in the VRET group showed higher adherence rates. This means that this therapy is useful for chronic patients. These conclusions should be taken with caution because the final sample size was small and data trends did not always reach statistical significance.[3]

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