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Efficacy of virtual reality exposure therapy combined with two pharmacotherapies in the treatment of agoraphobia[1]

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ABSTRACT. Currently, some psychopharmacological treatments, cognitive-behavioral therapies (CBT), and a combination of both are considered effective treatments for agoraphobia. Among psychological treatments, new therapeutic alternatives such as virtual reality exposure treatment (VRET) have been developed. The aim of this experimental study was to evaluate the efficacy of VRET combined with two antidepressant drugs (venlafaxine and paroxetine) in a sample of agoraphobia patients ($N = 64$), using a virtual system consisting of seven scenarios. Five types of treatment were compared: four combined treatment groups and one psychopharmacological treatment. Measures were taken at pre-treatment, post-treatment, and six-month follow-up; agoraphobia and anxiety measures were used as dependent variables. Results showed that all groups were statistically effective, both at post-treatment and six-month follow-up. However, based on clinical efficacy, results showed that combined treatment groups including VRET appeared to be better than traditional techniques at decreasing agoraphobia and anxiety measures and keeping them lower over time.

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KEY WORDS. Agoraphobia. Virtual reality. Cognitive-behavioral treatment. Pharmacological treatment. Experimental study.

RESUMEN. Actualmente, se consideran tratamientos eficaces para la agorafobia algunos psicofármacos, la terapia cognitiva conductual (TCC) y la combinación de ambos. Entre los tratamientos psicológicos se han desarrollado nuevas alternativas terapéuticas, tales como técnicas de exposición con realidad virtual (TERV). El objetivo de este estudio experimental ha sido evaluar, en una muestra de pacientes con agorafobia (N = 64), la eficacia de la TERV combinada con dos psicofármacos (venlafaxina y paroxetina), utilizando un sistema virtual formado por siete escenarios. Para ello, se compararon cinco tipos de tratamiento: cuatro grupos de tratamientos combinados y un grupo de tratamiento psicofarmacológico. Se tomaron medidas en el pre-tratamiento, post-tratamiento y en el seguimiento a los seis meses, y como variables dependientes se consideraron medidas de agorafobia y ansiedad. Los resultados mostraron que todos los grupos eran estadísticamente significativos, tanto en el postratamiento como en el seguimiento a los seis meses. Atendiendo a la eficacia clínica, los resultados mostraron que los grupos de tratamiento combinado con TERV disminuyeron las puntuaciones de agorafobia y ansiedad, manteniéndolas en el tiempo, más que las técnicas de tratamiento tradicional.

PALABRAS CLAVE. Agorafobia. Realidad virtual. Tratamiento cognitivo-conductual. Tratamiento farmacológico. Estudio experimental.

Agoraphobia is one of the most studied anxiety disorders because of its high lifetime prevalence rate (Bienvenue *et al*., 2006). It is characterized by resistance to spontaneous remission, comorbidity with other disorders, and impairment of quality of life. In addition, agoraphobia can have serious economic and social consequences, since a large percentage of people with agoraphobia suffer isolation and many of them are forced to leave their jobs (Mitte 2005; Tsao, Mystowski, Zucker, and Craske, 2005). This harmful consequence justifies the need for research on effective treatments.

Currently, some psychopharmacological treatments, cognitive-behavioral therapies, and a combination of both are considered effective treatments for agoraphobia (American Psychiatric Association, 2004; Echeburúa and Becoña, 2000; Echeburúa and Corral, 2001; Furukawa, Watanabe, and Churchill, 2006).

With regard to psychopharmacological treatment, the use of selective serotonin reuptake inhibitors (SSRIs) has been prioritized. These drugs have antidepressant and anxiolytic properties (Pae and Patkar, 2007). Among SSRIs, controlled studies show that paroxetine is an effective and well-

tolerated drug for the treatment of agoraphobia and panic disorder. Apart from paroxetine, other SSRIs such as sertraline, fluoxetine, citalopram and fluvoxamine have shown similar clinical results (Mochcovitch and Nardi, 2010). Venlafaxine, a serotonin and norepinephrine reuptake inhibitor (SNRI), has obtained good results with symptom remission in agoraphobia (Bradwejn *et al.*, 2005; de Abajo and García-Rodríguez, 2008; Ferguson, Khan, Mangano, Entsuah, and Tzanis, 2007; Kjernisted and McIntosh, 2007; Pollack *et al.*, 2007; Pollack, Mangano, Entsuah, Tzanis, and Simon, 2007; Pull and Damsa, 2008).

Among psychological treatments, cognitive behavioral therapy (CBT) and *in vivo* exposure have proven to be effective in reducing fear, anxiety, and agoraphobic avoidance. The role of cognitive change remains unclear (Hagenaars, van Minnen, and de Rooij, 2010); yet, combining exposure therapy (interoceptive and *in vivo*) with physiological deactivation techniques, such as relaxation techniques, breathing retraining or training in the management of anxiety, improves the efficacy of exposure to fear stimuli (Sánchez-Meca, Rosa-Alcázar, Marín-Martínez, and Gómez-Conesa, 2010).

Given the effectiveness of *in vivo* exposure therapies, new therapeutic alternatives to these tools have been developed, such as virtual reality exposure treatment (VRET). The use of VRET has been highlighted in the treatment of anxiety disorders, especially in specific phobias, where it has proven to be at least as effective as state-of-the-art *in vivo* exposure treatment (Choi, Fyer, and Lipsitz, 2007; de Carvalho, Freire, and Nardi, 2010; Gregg and Tarrier, 2007; Meyerbröker and Emmelkamp, 2010).

Few studies have explored the effect of VRET in the treatment of agoraphobia (de Carvalho *et al.*, 2010; Gregg and Tarrier, 2007; Meyerbröker and Emmelkamp, 2010). These studies have focused on the treatment of panic and agoraphobic avoidance behavior (Botella *et al.*, 2007; Choi *et al.*, 2005; Peñate, Pitti, Bethencourt, de la Fuente, and Gracia, 2008; Pérez-Ara *et al.*, 2010; Pitti *et al.*, 2008; Vincelli *et al.*, 2003). Although the results of these studies seem promising for VRET, further controlled studies are required to assess the effect of VR compared to traditional treatment; given that a group of these patients are medicated (often self-medicated), it is also necessary to test the ability of combined therapies (psychological and pharmacological) to reduce agoraphobia symptoms. Combined therapies have proven their efficacy both in the acute phase of treatment and the long term (Furukawa *et al.*, 2006).

In line with these studies and combined treatments to reduce agoraphobia symptoms, the aim of the present study was to evaluate the efficacy of new psychological procedures (virtual reality exposure) combined with some antidepressant drugs. To this end, in the context of CBT, the role of VRET combined with pharmacological treatment was tested in a sample of agoraphobia patients. Psychopharmacological treatment was performed with two of the most effective psychotropic drugs for this purpose: venlafaxine, an SNRI, and paroxetine, an SSRI.

Method

Participants

The study was carried out at the Psychiatric Service of the Canary Islands University Hospital (*Hospital Universitario de Canarias*, HUC). Participants were referred from mental health community units. Inclusion criteria for participants were meeting the criteria of the DSM-IV (American Psychiatric Association, 2000) and ICD-10 (World Health Organization, 1992) for the diagnosis of agoraphobia (with/without panic). Exclusion criteria were psychosis, personality disorders, and other anxiety disorders where agoraphobia disorder was a secondary diagnosis. All participants signed a consent form approved by the institutional ethics committee of the Canary Islands University Hospital. Initially, 106 people were screened for the study; 16 of them were excluded. Therefore, 90 patients with a diagnosis of agoraphobia (with/without panic) were included in this study. The mean age of the sample was 38.82 years (standard deviation – *SD* - = 10.75) and age ranged from 20 to 61 years. Most participants in the sample were women (63.30%). Regarding marital status, 40% were single, 50% were married, and 10% were divorced or separated. As for level of education, 15.60% had elementary education, 66.60% had secondary education, and 17.80% had a university degree. Evolution time with clinical symptoms ranged from 1 to 45 years, with a mean evolution time of 11.44 years (*SD* = 9.72). Evolution time was greater than 5 years in 67.80% of the cases.

Material and apparatus

Two instruments were used to verify the diagnosis of agoraphobia: a modified version of the composite International Diagnostic Interview -CIDI, 2.1- (Kessler and Üstün, 2004) and the Agoraphobia Inventory -AI-, based on behavioral-type phobic stimuli and their cognitive and physiological

concomitants (Echeburúa, Corral, García, Páez, and Borda, 1992). The first one (CIDI, 2.1) is a structured interview for major mental disorders, according to ICD-10 criteria (World Health Organization, 1992). Mental disorders are estimated both for lifetime and 12-month prevalence. In the present study we used CIDI 2.1 only to those questions and criteria related with agoraphobia. The second one (Agoraphobia Inventory-AI) measures a general level of agoraphobia, with 69 items, Likert scale. It is divided in two sections: the first part examines manifest behavior, cognitions, and psycho-physiology reactions, associated to agoraphobic situations (both, alone or with other people); the second part examines the response variations as a function of factors that increase and decrease agoraphobic behavioral patterns.

The following questionnaires and scales were administered to measure clinical symptoms and therapeutic progress:

- Body Sensations Questionnaire -BSQ- (Chambless, Caputo, Bright, and Gallagher, 1984). The BSQ is a self-reported questionnaire that contains 17 items rated on a 5-point Likert scale: 1 (*not worried*) to 5 (*extremely*). It assesses the frequency and level of an individual's fear of physical symptoms associated with panic disorder with agoraphobia. The final score is a calculation of the mean score of the 17 items. A high score indicates a greater fear of somatic symptoms. The Spanish translation of the BSQ questionnaire was used (Comeche, Díaz, and Vallejo, 1995).
- Agoraphobic Cognitions Questionnaire -ACQ- (Chambless *et al.*, 1984). The ACQ is a 14-item self-reported questionnaire based on a 5-point Likert scale: 1 (*I never think this*) to 5 (*always*). It assesses the frequency of catastrophic thoughts concerning the negative consequences of experiencing anxiety (fear of fear). Total scores on the ACQ are calculated by averaging responses to the individual items of the questionnaire. The Spanish translation of the ACQ was used (Comeche *et al.*, 1995).
- Beck Anxiety Inventory -BAI- (Beck, Epstein, Brown and Steer, 1988). The BAI is a 21-item multiple-choice self-report inventory that measures the severity of anxiety in adults and adolescents. It must be answered according to occurrence in the last week, on a 4-point scale (from *no to very*). The Spanish translation of the BAI was used (Sanz and Navarro, 2003).

In addition, the following instruments were used to assess self-perceived anxiety in patients compared to phobic stimuli: a measurement by which patients graded their degree of anxiety from 0 to 10 (Subjective

Units of Anxiety -SUA-) and a Behavioral Avoidance Test (BAT) in which patients were encouraged to cope with a real scenario similar to the virtual environments.

The Virtual Reality System and the software used in this study were the same as those used in studies by Peñate *et al.* (2008) and Pitti *et al.* (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 factorial experimental design (Montero and León, 2007; Ramos-Álvarez, Moreno-Fernández, Valdés-Conroy, and Catena, 2008) was used. This design included two independent variables. The first one was the different treatment modalities (six levels), and the second one was the lapse of time between the different measuring times (three levels). Therefore, a 6 *x* 3 design was used, considering six types of treatment: four combined treatments - CBT + paroxetine (n = 11); CBT + venlafaxine (n = 11); CBT-VRET + paroxetine (n = 11); CBT-VRET + venlafaxine (n = 11) - and two psychopharmacological treatments - paroxetine (n = 11) and venlafaxine (n = 9); the latter treatments were given to the groups in the waiting list for psychological treatment (WL) (Table 1). Measures were taken at three stages: pre-treatment, post-treatment, and six-month follow-up. The WL groups had measures taken only at the pre- and post-treatment stage. At the end of this phase, free psychological treatment was provided to those who requested it.

TABLE 1. Treatment modalities.

Pharmacological treatment	*Psychological treatment and WL*		
	CBT	*CBT-VRET*	*WL*
Paroxetine	11	11	11
Venlafaxine	11	11	9

Notes. CBT = cognitive behavioral therapy; CBT-VRET = cognitive behavioral therapy with virtual reality exposure; WL = waiting list.

The following measures were used as dependent variables: cognitive and overt behaviors related to agoraphobia, physiological reactivity, agoraphobic cognitions, general anxiety, and self-perceived anxiety.

Procedure

After an initial screening, the clinical psychologist in the team confirmed the diagnosis with the CIDI, 2.1 interview (Kessler and Üstün, 2004) and the AI (Echeburúa *et al.*, 1992). People who accepted to participate signed the informed consent and completed the pre-treatment measures. After this, patients were assigned to the different psychopharmacological treatment groups (paroxetine and venlafaxine). The psychiatrist in the team assessed patients' previous treatment and made psychopharmacological adjustments according to the psychodrug assigned. Patients in the paroxetine group received a dose between 20 and 30 mg/day, and patients in the venlafaxine group received a dose between 37.5 and 75 mg/day. Once patients had adapted to the new medication (after a month, approximately), they were randomly assigned to the different combined treatments groups or to the WL groups.

Each experimental group included 11 patients (combined treatment groups). The WL groups were composed of 9 patients taking venlafaxine and 11 patients taking paroxetine. The remaining 26 individuals did not belong to any combined treatment or psychopharmacological therapy groups because they left the study before the random assignment was made.

As regards psychotherapy, the experimental groups received 11 individual clinical sessions that lasted 30-45 minutes each. The first three sessions were similar in all conditions; they consisted of a psychoeducational session and two training sessions in cognitive restructuring. Sessions 4 to 11 were specific to the VR and CBT groups. Patients in the CBT groups were encouraged to confront phobic environments with *in vivo* exposure. In the VR groups, there was a combination of *in vivo* exposure and VR exposure sessions; patients

were exposed to the four virtual environments that had caused most anxiety in them. The 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 completed. Six months later, patients attended a psychological and psychiatric follow-up session and completed the follow-up measures.

Results

First, the dropouts were considered. Out of the 64 patients who were assigned to different groups, 12.50% of them discontinued at some stage of the study. According to dropout rates, no significant differences were found between the experimental groups ($\chi^2 = 14.47$; $p > .05$).

In order to determine whether the two WL groups (paroxetine and venlafaxine) could be treated as a single group, a t-test was carried out to compare pre-treatment and post-treatment measures between both WL groups. Given that no differences were found between both groups, they were considered as a single WL group.

After this, univariate ANOVAs and chi-square tests were used to assess the equivalence of participants in the five treatment conditions in terms of sociodemographic variables and clinical symptoms. Comparisons revealed no significant differences between the different groups.

Table 2 shows the mean and standard deviation of the different conditions for each outcome measure at post-treatment. Finally, a multivariate analysis of variance (MANOVA) was carried out to examine the effect of the five treatment groups at post-treatment.

Results show differences between groups (Hotelling Trace coefficient = .55, $F = 1.70$; $p < .05$). Multiple comparisons (Bonferroni adjustment) showed differences in the ACQ variable between the WL and the CBT-VRET + venlafaxine group. This value shows a trend in the CBT-VRET + venlafaxine group to obtain better results in agoraphobic cognitions compared to the WL group.

TABLE 2. Mean and standard deviation of the outcome measures at pre-treatment and post-treatment.

Measure		*CBT + paroxetine n (pre) = 11 n (post) = 11*		*CBT + venlafaxine n (pre) = 11 n (post) = 9*		*CBT-VRET + paroxetine n (pre) = 11 n (post) = 9*		*CBT-VRET + venlafaxine n (pre) = 11 n (post) = 10*		*WL n (pre) = 20 n (post) = 20*	
		M	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*
AI	Pre-treatment	218.60	79.35	221.36	47.10	229.50	66.10	242.18	73.20	206.90	58.10
	Post-treatment	129.50	79.8	144.80	101.08	132.10	77.30	132.40	52.90	200.50	73.60
ACQ	Pre-treatment	2.40	.90	2.70	.60	2.50	.50	2.50	.80	2.30	.60
	Post-treatment	1.60	.40	2.02	.90	1.90	.50	1.40	.20	2.10	.60
BSQ	Pre-treatment	2.90	.90	2.80	.60	3.10	.60	3.20	1.10	2.80	.80
	Post-treatment	2.40	.70	2.09	.80	2.10	.80	2.30	.70	2.60	.70
BAI	Pre-treatment	24.80	12.90	28.10	9.60	27	16.60	31	14	28.70	12.90
	Post-treatment	10.20	7.08	14.22	11.70	12.33	12.51	9.20	8.05	21.45	14.86

Notes. AI = Agoraphobia Inventory; ACQ = Agoraphobic Cognitions Questionnaire; BSQ = Body Sensations Questionnaire; BAI = Beck Anxiety Inventory; CBT + paroxetine = Cognitive behavioral therapy combined with paroxetine; CBT + venlafaxine = Cognitive behavioral therapy combined with venlafaxine; CBT-VRET + paroxetine = Cognitive behavioral therapy with virtual reality exposure combined with paroxetine; CBT-VRET + venlafaxine = Cognitive behavioral therapy with virtual reality exposure combined with venlafaxine; WL = Waiting list.

Repeated measures analyses of variance (ANOVAs) were performed to compare the efficacy between combined treatments in each dependent variable. Table 3 presents data showing the symptom reduction from pre-treatment, post-treatment and follow-up for the four combined treatment conditions, and the results of the repeated measures analyses of variance (ANOVAs).

TABLE 3. Mean and standard deviation of the outcome measures and ANOVA results.

Measure		*Pre-treatment*		*Post-treatment*		*Follow-up*		*Time effect*		*Treatment x Time interaction*		*Treatment effect*	
		M	*SD*	*M*	*SD*	*M*	*SD*	*F*	*p*	*F*	*p*	*F*	*p*
AI	CBT + paroxetine (n = 11)	218.60	79.30	129.50	79.80	134	96.70	49.60	.000	1.09	.37	1.97	.89
	CBT + venlafaxine (n = 7)	218.80	55.40	158.10	111.70	126.20	74.80						
	CBT-VRET + paroxetine (n = 8)	224.70	77.50	121.80	75.90	89.30	71.70						
	CBT-VRET + venlafaxine (n = 10)	228.60	60.80	132.40	52.90	84	89.80						
ACQ	CBT + paroxetine (n = 11)	2.40	.90	1.60	.40	1.70	.80	27.91	.000	.70	.64	.74	.53
	CBT + venlafaxine (n = 7)	2.70	.70	2.10	1.02	1.80	.90						
	CBT-VRET + paroxetine (n = 8)	2.50	.60	1.90	.50	1.50	.70						
	CBT-VRET + venlafaxine (n = 10)	2.30	.40	1.40	.20	1.60	.60						
BSQ	CBT + paroxetine (n = 11)	2.90	.80	2.40	.70	2.30	1.10	17.67	.000	.28	.94	.16	.92
	CBT + venlafaxine (n = 7)	2.90	.70	2.20	.90	2.07	.90						
	CBT-VRET + paroxetine (n = 8)	3.10	.60	2.05	.70	2.10	.80						
	CBT-VRET + venlafaxine (n = 10)	3.05	1.03	2.30	.70	2.30	.90						
BAI	CBT + paroxetine (n = 11)	24.80	12.90	10.20	7.08	9.90	7.90	34.20	.000	.19	.97	.71	.55
	CBT + venlafaxine (n = 7)	32	9.10	15.50	13.07	18.70	14.12						
	CBT-VRET + paroxetine (n = 8)	25.30	19.30	10.60	12.20	11.25	18.70						
	CBT-VRET + venlafaxine (n = 10)	28.60	12.20	9.20	8.05	12.20	16.30						

Notes. AI = Agoraphobia Inventory; ACQ = Agoraphobic Cognitions Questionnaire; BSQ = Body Sensations Questionnaire; BAI = Beck Anxiety Inventory.

ANOVAs performed on clinical symptom variables (general level of agoraphobia, physiological reactivity, agoraphobic cognitions, and general level of anxiety) revealed a highly significant time effect for all dependent variable measures. However, comparisons revealed that the treatment *x* time interaction did not differ in any outcome variable. A repeated measures analysis of variance (ANOVAs) with twelve levels (11 psychotherapy sessions and a follow-up session) was performed on the Subjective Units of Anxiety (SUA). Although results showed a time effect ($F_{(10, 180)} = 7.25$; $p < .05$), again, the treatment *x* time interaction was not significant.

For the BAT test, a total of 12 patients were selected from the four combined treatment groups. With the help of a therapist, patients were exposed to two of the following scenarios: an airport building, a square and a street, an elevator and an underground car park, a bank office, and a highway[3]. Table 4 shows the means and sample sizes of the BAT measures obtained. Only the CBT-TERV + venlafaxine group obtained scores below 2.5 points in both scenarios.

TABLE 4. Means and sample sizes of Behavioral Avoidance Test (BAT) measures.

		SCENARIO 1				*SCENARIO 2*	
Treatment modality	*n*	*Time (Mean)*	*SUA (Mean)*	*Treatment modality*	*n*	*Time (Mean)*	*SUA (Mean)*
CBT + paroxetine	2	15	5.25	CBT + paroxetine	2	12.50	0
CBT + venlafaxine	2	15	3.5	CBT + venlafaxine	2	20	4.25
CBT-VRET + paroxetine	4	16.25	4.25	CBT-VRET + paroxetine	3	15	1.33
CBT-VRET + venlafaxine	4	20	2.27	CBT-VRET + venlafaxine	3	16.66	1.66

[3] Due to difficulties in accessing to the cableway and beach scenarios, it was not possible to include these scenarios.

Discussion

The aim of this study was to evaluate the effectiveness of combined treatments for agoraphobia in a sample of 90 patients with a mean evolution time of 11.44 years. This involved testing the use of VR techniques, with a virtual system consisting of seven scenarios, and comparing them with the use of traditional cognitive-behavioral treatment. Both psychological techniques were combined with pharmacological treatment using venlafaxine, a serotonin and norepinephrine reuptake inhibitor (SNRI) and paroxetine, a selective serotonin reuptake inhibitor (SSRI).

Results of within-group comparisons at post-treatment and six-month follow-up showed improvement in all groups over time, including the group treated only with psychotropic drugs. Between-group comparisons showed no significant differences, that is, no experimental groups proved to be more effective than the rest.

However, these results should be considered taking into account the size of the study sample. The analyses of variance performed in the present study have very little statistical power, so it is difficult to interpret significant results realistically. Therefore, further interpretation of the results is required. For this reason, because the comparison between the average scores on each variable showed that symptoms decreased more in some groups than others, differential levels of clinical improvement were analyzed (pre-treatment scores minus post-treatment scores, and pre-treatment scores minus six-month follow-up scores). Thus, according to the data shown in tables 2 and 3, clinical improvement was considered to occur when the scores of variables decreased by 50% compared to pre-treatment scores. Table 5 identifies groups with differential levels of clinical improvement in some of the study variables. The WL group did not obtain a 50% reduction in any of the variables. In contrast, agoraphobia symptoms (AI) decreased by more than 50% in both combined treatment groups with VR (CBT-VRET + paroxetine and CBT-VRET + venlafaxine) compared to the CBT groups (CBT + paroxetine and CBT + venlafaxine). However, reductions in the ACQ and BSQ measures did not reach 50% in all groups. Regarding the general measure of anxiety (BAI), all groups achieved a 50% reduction at post-treatment, whereas only the CBT + venlafaxine group did not reach this reduction at six-month follow-up. Regarding self-perceived anxiety at the post-treatment, the combined treatment paroxetine groups (CBT-VRET + paroxetine and CBT + paroxetine) achieved the greatest reduction. At six-month follow-up, all groups continued to improve except for the CBT + venlafaxine group.

TABLE 5. Variables that decreased their scores by 50% between pre-treatment and post-treatment, and pre-treatment and follow-up.

Measure		*CBT + paroxetine*	*CBT + venlafaxine*	*CBT-VRET + paroxetine*	*CBT-VRET + venlafaxine*	*WL*
AI	Post-treatment					
	Follow-up			X	X	
ACQ	Post-treatment					
	Follow-up					
BSQ	Post-treatment					
	Follow-up					
BAI	Post-treatment	X	X	X	X	
	Follow-up	X		X	X	
SUA*	Post-treatment	X		X		
	Follow-up	X		X	X	

Notes. AI = Agoraphobia Inventory; ACQ = Agoraphobic Cognitions Questionnaire; BSQ = Body Sensations Questionnaire; BAI = Beck Anxiety Inventory; SUA = Subjective Units of Anxiety.
* For the SUA measures, the measurements obtained at the end of psychotherapy sessions and at follow-up were taken into account.

A comparison between the present study and previous studies shows some similarities and differences. First, it shows that the sample used in this study is larger than those used in previous studies on VR. In addition, the present study is the first to compare the use of VR combined with two types of psychoactive drugs. The use of two drugs is in line with previous studies indicating that both paroxetine and venlafaxine are effective in the treatment of agoraphobia (Pollack, Lepola *et al.*, 2007; Pollack, Mangano *et al*., 2007) and show better results when combined with psychological treatment.

As regards follow-up, there are similarities with other studies that have considered this measure. A few examples are the study by Peñate *et al.* (2008), with three-month follow-up, that of Choi *et al.* (2005), with six-month follow-up, and the study by Botella *et al.* (2007), with one-year follow-up. The present results agree with those of Pitti *et al.* (2008) and Botella *et al.* (2007) in that they show that combined therapy groups including VR techniques obtain greater improvements than traditional therapy groups.

Virtual scenarios in this research included seven local scenarios, as in the studies by Peñate *et al.* (2008), Pitti *et al.* (2008), and Botella *et al.* (2007), which included different virtual scenarios, although they were not all local. Previous studies only used one type of scenario (Choi *et al.*, 2005; Vincelli *et al.*, 2003).

In addition to the contributions made by this study, a few limitations must be considered. The most important one is the sample size of patients. Although the present sample was larger than the sample used in previous

studies, the number of patients in each treatment group was never greater than 20. Another limitation is the number of virtual scenarios. Even though they were local scenarios and therefore more realistic, given the complexity of agoraphobia and the variability of anxiogenic situations for a patient with agoraphobia, the number of scenarios was probably insufficient.

In future research, it would be interesting to study the psychological variables that play an important role in assessing virtual environments and facilitate the activation of emotions during exposure. Furthermore, these combined treatments (CBT-VRET and psychotropic drugs) should be compared in a larger sample, in order to make comparisons with greater statistical power. It is also necessary to compare combined treatment groups with a group without any psychopharmacological therapy. Similarly, it would be interesting to have a larger number of VR exposures in the package of exposure sessions of VR groups.

In conclusion, the results of the study show that all groups are statistically effective, both at post-treatment and six-month follow-up. However, based on clinical efficacy, the results show that combined treatment groups with VRET appear to be better than traditional techniques at decreasing agoraphobia and anxiety measures and keeping them lower over time. In addition, they show that the use of the antidepressants paroxetine (SSRI) and venlafaxine (SNRI) decreases agoraphobia symptoms when combined with psychological techniques (including VRET).

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