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# Agoraphobia: combined treatment and virtual reality. Preliminary results

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**Introduction.** Several validation studies have identified the use of certain psychodrugs, cognitive-behavioral therapy (CBT) and combined treatment as effective procedures for the treatment of agoraphobia. Recent findings suggest that agoraphobia can also be treated with virtual reality techniques (VRET) as an alternative exposure technique to virtual reality stimuli.

**Methodology.** Twenty-seven patients with agoraphobia were distributed into two groups of psychoactive drugs (paroxetine and venlafaxine) and into two cognitive-behavioral procedures (with or without exposure to VRET). Seven virtual situations were used.

**Results.** Preliminary results show significant improvements in all the experimental groups. Regarding the psychodrugs (paroxetine and venlafaxine) both significantly improved the symptoms and in regards to the CBT, patients treated with VRET, especially the chronic patients, seem to obtain the best results.

**Conclusions.** Agoraphobia combined treatments including paroxetine, venlafaxine and cognitive-behavioral therapy (with or without VRET) seem to have clear benefits for the patients. VRET seem to be a possible and effective treatment for agoraphobic patients, especially for those with chronic agoraphobia.

**Key words:**
Agoraphobia. Paroxetine. Venlafaxine. Virtual reality. Mixed treatments.

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## Agorafobia: tratamientos combinados y realidad virtual. Datos preliminares

**Introducción.** Diversos estudios de validación han identificado el uso de ciertos psicofármacos, las terapias cognitivo-conductuales (TCC) y los tratamientos combinados como procedimientos eficaces para el tratamiento de la agorafobia. Investigaciones recientes sugieren que la agorafobia puede ser abordada también con procedimientos como terapia de exposición a realidad virtual (TERV) los escenarios fóbicos.

**Metodología.** Veintisiete pacientes con agorafobia fueron distribuidos en dos grupos de psicofármacos (paroxetina y venlafaxina) y en dos procedimientos cognitivo-conductuales (con o sin exposición a TERV). Se utilizaron siete escenarios virtuales.

**Resultados.** Se observan mejorías clínicamente significativas en todos los grupos experimentales. Respecto a los psicofármacos (paroxetina y venlafaxina), ambos mejoran significativamente la sintomatología, y en lo que a las TCC se refiere, los pacientes tratados con TERV parecen beneficiarse en mayor medida, especialmente los crónicos.

**Conclusiones.** Los tratamientos combinados para la agorafobia, incluyendo paroxetina, venlafaxina y técnicas cognitivo-conductuales (con o sin TERV), parecen mostrar beneficios clínicos. Las TERV parecen ser un posible tratamiento eficaz para la agorafobia, especialmente para los pacientes con agorafobia crónica.

**Palabras clave:**
Agorafobia. Paroxetina. Venlafaxina. Realidad virtual. Tratamientos combinados.

## INTRODUCTION

Studies on treatment of agoraphobia have identified certain psychodrugs, psychotherapy and the combination of both resources - combined treatments, as effective procedures to treat agoraphobia[1-3].

In treatment with psychodrugs, selective serotonin reuptake inhibitors (SSRI, paroxetine) and serotonin-norepinephrine reuptake inhibitors (SNRI, venlafaxine, dose dependent > 75 mg/day) are showing greater efficiency compared to the traditional anxiolytics and tricyclic antidepressants (TAD)[4-5]. Furthermore, these psychodrugs have better tolerance levels, since they do not cause as many anticholinergic

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effects, do not seem to generate vascular alterations and do not tend to favor weight gain. Thus, in recent years, they have become the psychopharmacological treatment of first choice for panic disorders and agoraphobia. The use of paroxetine in the treatment of agoraphobia is well established, while venlafaxine seems to be progressively becoming another preferential psychodrug for the treatment of this disorder[6-8].

In regards to the psychological approach to agoraphobia, there are two treatments that have demonstrated their efficacy: *in vivo* exposure and cognitive-behavior therapies[9-10]. *In vivo* self-exposure and/or exposure implies that the patient is exposed to the feared phobic stimuli gradually. Cognitive-behavior treatments consist in treatment packages that generally include psychoeducation on the disorder, cognitive restructuring, interoceptive exposure, *in vivo* exposure, controlled breathing and relaxation[11]. Effective psychological treatments include techniques of exposure to phobic stimuli, central mechanism of therapeutic change, as concurrent element.

As these treatments are effective, these same references indicate high level of discontinuity, lack of compliance, drop-outs and relapses as one of the most relevant problems. Recent lines of research indicate greater efficacy and compliance with combined treatments - cognitive-behavior therapy and psychodrugs[12-14]. The drug would act on the reduction of the symptoms and psychological treatments on increase of competences[15]. Thus, combined therapy may be especially useful in the most serious cases. In these cases, patients with agoraphobia (PA) finally stay at home, which makes it especially difficult to use *in vivo* exposure as an effective psychological technique. That is why the use of phobic scenarios constructed with virtual reality techniques has become a useful procedure to expose patients to phobic stimuli similar to those of real situations.

The idea of using virtual reality (VR) technologies to treat psychological disorders was developed for the first time in the Human-Computer Interaction Group of Clark University of Atlanta[16]. They coined the term Virtual Reality Therapy (VRET) and used this technique to treat phobia of flying in a single case design and with clinically significant results. Since then, VRET has been used to treat different specific phobias (flying claustrophobia, driving, speaking in public, etc.). It has been shown to be as effective as other therapeutic procedures[17,18], and has the additional advantage that it is used as a simulated system.

Specifically, there are very few studies on agoraphobia. The reason that there are so few publications may be due to the fact that agoraphobia is the most complex phobia, made up by a combination of phobias where both virtual and possible phobias settings are necessary. Access to multiple virtual settings makes the research works substantially more expensive and thus restricts the possibility of accessing this type of clinical-experimental works. In spite of this, some research has been done, obtaining unequal results. Thus, North, North and Coble (1996)[19] worked with a subclinical sample of students who fulfilled criteria for agoraphobia, showing the efficiency of exposure to virtual reality only in some of the variables considered. The worst results were obtained by Jang, Ku, Shin, Choi and Kim (2000)[20] who, as indicated by the authors, did not achieve the sensation of presence in their virtual scenario and stopped the research.

Recent publications in the area have shown a series of improvements in the design and procedure (VR quality, clinical samples, type of disease-acute/chronic, number of treatment sessions and their duration, combined use with other treatments, etc.). These research works suggest that agoraphobia can be treated with virtual reality exposure treatment (VRET)[17,21-24].

Based on the above expressed, this present research work aims to present the first results obtained in the treatment of a clinical sample of agoraphobia patients, combining traditional cognitive-behavior treatments (CBT), cognitive-behavior treatments with VR (VRET) and two psychodrugs: selective serotonin reuptake inhibitors (SSRI, paroxetine) compared to a selective serotonin-norepinephrine reuptake inhibitor (SNRI, venlafaxine, dose dependent >75 mg/day). In the second place, it aims to investigate if the VRET procedures are especially useful in the cases that have greater chronicity.

## METHODOLOGY

### Participants

The participants were AP referred from the Mental Health Units of the two health care professional groups of the Island of Tenerife (Health Care Consortium of Tenerife and Canary Island Service of Health) to the out-patient Agoraphobia Unit of the University Hospital of the Canary Islands. The initial sample was made up of the first 39 participants with agoraphobia under treatment who had initiated psychotherapy. Twelve of them dropped out of the study (31%). These drop-outs were considered to be related with experimental variables, verifying that they were not due to any parameter considered.

In regards to gender and age variables, our study sample was mostly made up of women (22 patients) and the mean age of the group was 38.5 years (±9.3). In regards to civil status, 14 were married, 9 single and 4 separated/divorced. Regarding education level, 7 had university degrees, 16 high school degrees and 4 primary education.

In regards to the diagnosis, 20 cases fulfilled criteria for agoraphobia with panic and 7 agoraphobia without panic. For the secondary diagnosis, 18 cases had other comorbid disorders (14 with mood state disorders and 4 with anxiety

disorders). Evolution time with the clinical pictures was within a range of 1 to 30 years, with mean evolution time of 9.1 years and standard deviation of 7.8 years. Evolution time was between 2 and 11 years in 50% of the cases.

Those patients who suffered psychotic pictures or bipolar disorders, those who had elevated suicidal risks, who had cardiac, neurological (epilepsy type) and ophthalmologic (on the level of binocular vision that made stereoscopic vision difficult) were excluded.

## Material and apparatuses

Different instruments were used to evaluate the sample initially and to compare therapeutic efficacy.

The CIDI interview (modular 2.1, modified version) was used for the diagnosis. Furthermore, the Hamilton Anxiety Scale[25] and Agoraphobia Inventory[26] (AI, based on behavioral type phobic stimuli and their cognitive and physiological concomitants) were used to strengthen the diagnostic decision making.

To measure symptoms and therapeutic progress, the following questionnaires and scales were administered: the Body Sensations Questionnaire, BSQ[27], to measure self-reported physiological reactivity; the Agoraphobic Cognitions Questionnaire, ACQ[27], to measure negative thoughts in agoraphobia; the Behavioral Scale of Agoraphobic Maladaptive Coping, CAD[28], to measure maladaptive coping that the patients have towards phobic and interoceptive stimuli and that frequently consist in ritualistic, superstitious, safety seeking, etc. behaviors (separated into two measurements: manifest and masked behaviors): the Beck Anxiety Inventory, BAI[29], as a general measure of anxiety and the Beck Depression Inventory, BDI-II[30], as a general measure of depression. Furthermore, the AI was used as a pre- and post-test measurement. In addition, subjective units of anxiety (SUA), a measurement by which the patients graded their degree of anxiety from 0 to 10 generated by *in vivo* exposures to the phobic stimuli, were included.

The Virtual Reality System was made up of a passive stereoscopic video-projection system that used two 3000 lumen DLP type video-projectors, with light polarization and passive polarized glasses. The video-projectors generated a stereoscopic image on a screen, with a special coating for polarized light, which was placed in front of the patient, covering all the wall of the room. An attempt was made to simulate a cave type setting. The patient used glasses and moved with a joystick.

The computers used to control the system had a high quality graphic plaque, with hardware support for the generation of stereo images (quad-buffered stereo). OpenGL with stereo support, was used a graphics library. The signal generated by the graphic plate was active stereo and was sent to a demultiplexor that transformed it into two passive phase signals, which attacked each one of the DLP projectors, thus obtaining the desired effect.

The software was developed with seven local prototypical scenarios (fig. 1) of the agoraphobic stimuli. Each patient was exposed to a neutral scenario of adaptation to the system and 3 of the 7 scenarios (the most feared). The first scenario represents a line in a bank office, the second one represents a square joined to a centrally situated and crowded pedestrian street, the third one is a centric parking, the fourth represents the airport of the north of the island and the boarding of a plane, the fifth is a little visited beach in the south of the island, the sixth is a trip by car in a highway with much traffic and the seventy is a trip in the cable car of Teide. All the scenarios have the difficulty to abandon the situation and the lack of nearby health care centers in common.

## Design and procedure

A 2×2 mixed design was used. It had two psychodrugs (paroxetine, SSRI, and venlafaxine, SNRI) and two psychological therapies (traditional cognitive-behavioral therapy, CBT, and virtual reality cognitive-behavioral therapy, VRET). Based on the type of psychodrug, the sample was constituted by 12 patients under treatment with SSRI (mean group dose of 26.66 mg/day) and 15 cases under treatment with SNRI (mean group dose of 91.07 mg/day) and they initiated psychotherapy 4-6 weeks after the treatment onset. On the other hand, and according to the type of psychological treatment, 18 out of the 27 participants belonged to the VRET treatment group and 9 to the CBT treatment. This initial inequality in the distribution of the groups is justified by the drop-outs since the computer program assigned the AP to the different groups in the initial phases.

The independent variable «type of treatment» was analyzed using within group and between group comparisons, with pre-and post-treatment measurements.

### *Procedure*

Initially, the clinical psychology confirmed the diagnosis with an interview (CIDI, modular 2,1 version, modified) and with different diagnostic tests and after a protocol of informed consent was signed, the patients were randomly assigned to the different treatment groups. The patients were assigned by a computer programs designed for this study, homogenizing the groups based on the variables of gender, age and evolution time. After, the psychiatrist of the unit assessed the patient's treatment and made psychopharmacological adjustments according to the psychodrug assigned by the computer. Once the patient had adapted to the new

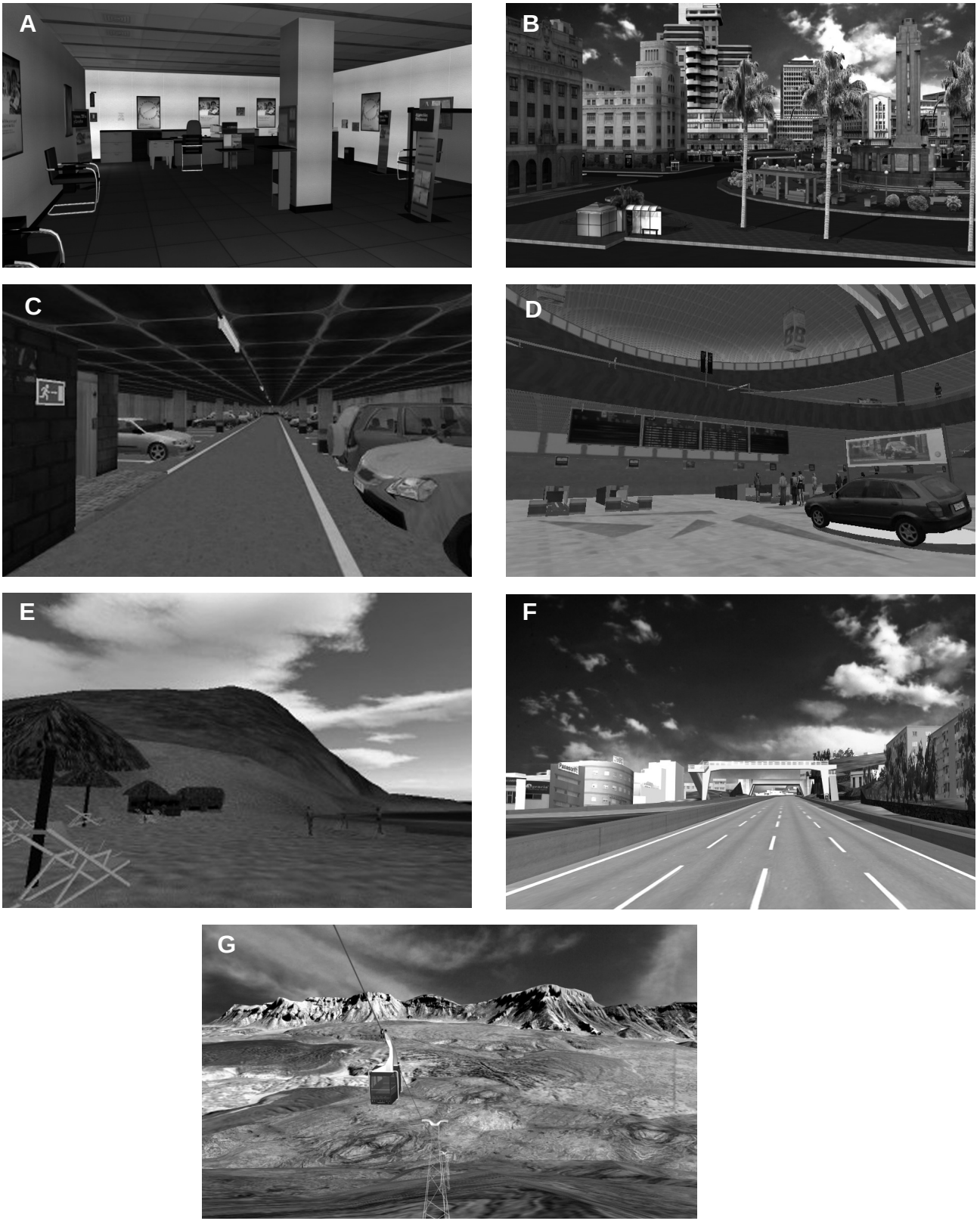


**Figure 1** *Photographs of the seven virtual scenarios.* **A)** *Bank office.* **B)** *Plaza de España.* **C)** *Garage and parking plaza Weyler.* **D)** *Airport Tenerife Norte.* **E)** *Beach of La Tejita.* **F)** *Highway Santa Cruz-Laguna.* **G)** *Cable car of Teide.*

medication, he/she was sent to the psychologist again to initiate psychotherapy.

Regarding psychotherapy, both clinical-experimental groups received 11 individual clinical sessions of 30 minute long psychotherapy (weekly), the first three sessions being similar in both conditions, making up one psychoeducational session and two training sessions in cognitive restructuring. Starting with the fourth session and until the eleventh one, one group received eight follow-up sessions versus *in vivo* hierarchized self-exposure therapy (CBT) while the other group (VRET) received 4 therapy sessions of exposure to virtual reality (from 10-12 minutes) and 4 follow-up sessions of *in vivo* hierarchized self-exposure therapy (alternate). Both experimental groups were motivated to practice *in vivo* self-exposure. As dependent variables, there were different measurements of inventories, self-reports and behavior recording that included the subjective units of anxiety (SUAs).

Two therapists (psychiatrist and psychologist), with wide experience in the treatment of agoraphobia, directed all the interventional phase with the objective of minimizing unwanted experimental biases.

Due to the small sample size, the statistics contrasts used were non-parametric (Mann-Whitney U test for independent samples and Wilcoxon T for related samples). For the SUAs contrasts, the initial average values towards phobic stimuli and final values (session 11) were used.

## RESULTS

A first group of analysis was performed to compare pre-treatment measurements between the different groups, divided according to the type of psychodrug and according to type of psychological treatment, for all the variables evaluated (Mann-Whitney U test). No significant differences were found between the different groups, except in the general score in agoraphobia (questionnaire IA), while the paroxetine group began with a significantly higher score. Therefore, in general, it can be considered that the groups were initially basically homogeneous.

A second group of analysis was conducted in order to evaluate if the different treatment groups had improved, comparing the pre-treatment levels with the post-treatment ones. On the one hand, the effect of the psychodrugs (paroxetine and venlafaxine) was compared and on the other, the effect of the type psychological treatment types (CBT and VRET) were compared. Table 1 summarizes the significance levels of the before and after analysis performed for each treatment type. It should be pointed out that all these comparisons are expressed according to how they cause a decrease in the disease.

As can be observed, in the case of psychodrugs, both seem to demonstrate elevated improvement, comparing the before and after results of the treatment. However, this effect is generalized for venlafaxine (decrease the general level of agoraphobia, negative physiological activation, agoraphobic cognitions, behaviors and maladaptive cognitions, anxiety experienced when faced with the phobic stimuli, including a significant decrease in the general level of anxiety and depression). On the contrary, in the case of paroxetine, this does not seem to affect the partial copings (there was no decrease in the strategies having a ritualistic, superstitious character, signs of safety, etc., that the agoraphobic patients use to cope with phobic stimuli).

In regards to the two psychological treatments, something similar to that which occurs with the psychodrugs occurs. Both treatments tend to have levels of elevated improvement. However, while the therapy aided by virtual reality technology seems to show its efficacy in all the measurements, the traditional CBT fails to decrease the manifest behaviors of maladaptive coping.

Based on the previous data, the following group of analysis compared the post-treatment effects, considering, on the one hand, the effects of venlafaxine versus paroxetine and, on the other, the effects of CBT versus VRET. Analyzing the mean post-treatment scores, no significant differences were found between the two psychodrugs and two psychotherapy procedures, except some marginal difference: a greater decrease of the level of general anxiety in the paroxetine group compared to the venlafaxine one ($p \leq 0.04$) and a greater decrease of maladaptive cognitions of the VRET group versus the CBT one ($p \leq 0.03$). Thus, it could be stated that both groups improved in a similar way. It should be mentioned that some mean scores are clearly different. However, the reduced size of the groups did not make it possible for these differences to be statistically significant.

**Table 1** **Pre and post-treatment statistical significance levels for the different types of treatments, obtained in the Wilcoxon rank sum test**

| | IA | BSQ | ACQ | CAD (Motor) | CAD (Cogn.) | BAI | BDI-II | SUA |
|---|---|---|---|---|---|---|---|---|
| Paroxetine | 0.002 | 0.012 | 0.001 | 0.082 | 0.175 | 0.001 | 0.004 | 0.040 |
| Venlafaxine | 0.007 | 0.012 | 0.001 | 0.015 | 0.0001 | 0.001 | 0.0001 | 0.045 |
| CBT | 0.036 | 0.007 | 0.007 | 0.137 | 0.043 | 0.017 | 0.010 | 0.057 |
| VRET | 0.001 | 0.006 | 0.0001 | 0.006 | 0.001 | 0.0001 | 0.0001 | 0.032 |

AI: agoraphobia index; BSQ: body sensations questionnaire; ACQ: agoraphobic cognitions questionnaire; CAD (Motor): maladaptative coping behaviors manifested; CAD (Cogn.): agoraphobic maladaptive coping; BAI: Beck anxiety inventory; BDI-II: Beck depression level; SUA: subjective units of anxiety to phobic stimuli; CBT: behavioral-cognitive treatment; VRET: CBT with exposure to virtual scenarios.

A last group of analyses was conducted in order to determine what type of psychotherapy would be most beneficial for each type of AP based on time of evolution, comparing acute patients (AG) to the chronic ones (CR). As you may remember, the VRET was expected to be especially useful with chronic agoraphobia because of the difficulties of these patients to expose themselves *in vivo* to phobic stimuli. These are tentative data due to the small number of patients per group. However, as can be observed in table 2, the AP of the VRET group are the ones who obtain the best results. In the case of the patients with acute disease, the CBT do not show significant results. However, VRET seems to improve the AP in the general measurements of agoraphobia, anxiety and depression, in agoraphobic cognitions and in the use of maladaptive behaviors. These results are even more significant with chronic disease, where which the patients who received VRET therapy showed improved in almost all the indexes (except the SUA) and with very elevated significance levels. Thus, this favors the prediction that this group of chronic patients would be the ones who would benefit the most from a procedure of exposure to virtual reality (table 2).

## DISCUSSION AND CONCLUSIONS

The therapeutic approach to agoraphobia is presently well established both with psychodrugs as well as with psychotherapies. However, there are still some problems, among them, the high level of drop-outs from therapy, relapses, accompanied by side effects of some drugs and the difficulty that the chronic AP have to undergo exposure therapy to phobic stimuli. The use of dual drugs and the application of new technologies as well as virtual reality have tried to alleviate such effects[4-8,17-24, 31].

This present research work used a combined treatment of two drugs (SSRI and SNRI) with two psychological treatments (CBT and VRET). The within group results seem to show significant improvements preliminarily, both when the psychodrugs are taken separately as well the psychological treatments are done separately.

Specifically, venlafaxine seems to have shown similar efficacy to paroxetine, with the difference that the latter did not produce a significant decrease of maladaptive cognitions, strategies which seem to play an important role in the chronification of the proble[28]. In the case of the psychological treatments, the use of VRET seems to be strengthened, especially with chronic AP: VRET shows better results compared to tradition CBT. This may be due to the improvement that is found in the use of virtual reality as an exposure technique for these patients with significant mobility limitations.

In the second place, another datum of interest is the high level of drop-outs produced with the CBT compared to the VRET one. The reasons for this may be found in the clear novelty entailed by the use of virtual reality as an attraction value itself. However, it is also possible that the patients are better controlled by a procedure which is a good middle stage for real coping with phobic stimuli.

**Table 2** Post-treatment values, within group means and statistical significant obtained in the Mann-Whitney U test, when considered according to the type of psychodrug and type of psychotherapy

| | Venlafaxine | Paroxetine | p | CBT | VRET | p |
|---|---|---|---|---|---|---|
| AI | 25.50 | 20.50 | 0.352 | 60.00 | 61.50 | 0.876 |
| BSQ | 44 | 22 | 0.067 | 36.30 | 40.11 | 0.464 |
| ACQ | 34.50 | 31.50 | 0.571 | 24.90 | 20.78 | 0.135 |
| CAD (Motor) | 36.50 | 29.50 | 0.439 | 108.20 | 97.83 | 0.573 |
| CAD (Cogn.) | 38 | 28 | 0.788 | 71.20 | 51.44 | 0.036 |
| BAI | 38 | 28 | 0.044 | 22.40 | 14.78 | 0.062 |
| BDI-II | 34.50 | 31.50 | 0.368 | 14.80 | 12.83 | 0.597 |
| SUA | 2.3 | 2.2 | 0.236 | 2.61 | 1.90 | 0.626 |

AI: agoraphobia index; BSQ: body sensations questionnaire; ACQ: agoraphobic cognitions questionnaire; CAD (Motor): maladaptative coping behaviors manifested; CAD (Cogn.): agoraphobic maladaptive coping; BAI: Beck anxiety inventory; BDI-II: Beck depression level; SUA: subjective units of anxiety to phobic stimuli; CBT: behavioral-cognitive treatment; VRET: CBT with exposure to virtual scenarios; p: statistical significance level.

**Table 3** Levels of statistical significance ($p \leq 0.05$) pre and post-treatment, obtained in the Wilcoxon rank sum test based on evolution time and type of psychotherapy

| | IA | BSQ | ACQ | CAD (Motor) | CAD (Cogn.) | BAI | BDI-II | SUA |
|---|---|---|---|---|---|---|---|---|
| AC-CBT | 0.223 | 0.080 | 0.068 | 0.500 | 0.893 | 0.138 | 0.068 | 10.00 |
| AC-VRET | 0.028 | 0.130 | 0.029 | 0.091 | 0.016 | 0.005 | 0.003 | 0.063 |
| CR-CBT | 0.043 | 0.043 | 0.080 | 0.080 | 0.043 | 0.068 | 0.138 | 0.069 |
| CR-VRET | 0.018 | 0.018 | 0.018 | 0.028 | 0.018 | 0.043 | 0.018 | 0.109 |

AI: agoraphobia index; BSQ: body sensations questionnaire; ACQ: agoraphobic cognitions questionnaire; CAD (Motor): maladaptative coping behaviors manifested; CAD (Cogn.): agoraphobic maladaptive coping; BAI: Beck anxiety inventory; BDI-II: Beck depression level; SUA: subjective units of anxiety to phobic stimuli; AC-CBT: acute patients-cognitive-behavioral treatment; AC-VRET: acute patients CBT with exposure to virtual scenarios; CR-CBT: chronic patients-cognitive-behavioral treatment; CR-VRET: chronic patients-CBT with exposure to virtual scenarios.

Clearly, these results are only tentative ones due to the limited design and sample. Larger samples and groups with different contrasts (treatments done separately with psychodrugs, psychotherapy and both compared to the combined treatments, groups from waiting lists and differentiation by acute versus chronic disease) are needed. Furthermore, middle and long term follow-up should be included to know the consolidation grade of these results. Specifically, more research works that include more virtualized scenarios are necessary for VRET. Ideally, these works should have as many agoraphobic stimuli as possible.

However, considering the preliminary results described, we could tentatively conclude that our system that includes techniques of exposure to virtual reality seems to tend to become a possibly effective treatment (in the context of combined treatment), especially useful for patients with chronic agoraphobia.

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