The combined use of virtual reality exposure in the treatment of agoraphobia

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Introduction. This study compares the differential efficacy of three groups of treatments for agoraphobia: paroxetine combined with cognitive-behavioral therapy, paroxetine combined with cognitive-behavioral therapy and virtual reality exposure, and a group with only paroxetine.

Methodology. 99 patients with agoraphobia were finally selected. Both combined treatment groups received 11 sessions of cognitive-behavioral therapy, and one of the groups was also exposed to 4 sessions of virtual reality treatment. Treatments were applied in individual sessions once a week for 3 months.

Results. The three treatment groups showed statistically significant improvements. In some measures, combined treatment groups showed greater improvements. The virtual reality exposure group showed greater improvement confronting phobic stimuli.

Conclusions. Treatments combining psychopharmacological and psychological therapy showed greater efficacy. Although the use of new technologies led to greater improvement, treatment adherence problems still remain.

Keywords: Agoraphobia, Combined treatment, Paroxetine, Psychotherapy, Virtual reality

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El uso combinado de la exposición a realidad virtual en el tratamiento de la agorafobia

Introducción. Este estudio compara la eficacia diferencial de tres grupos de tratamiento para la agorafobia: paroxetina en combinación con terapia cognitivo-conductual, paroxetina en combinación con terapia cognitivo-conductual y exposición de realidad virtual, y un grupo sólo con paroxetina.

Metodología. Fueron seleccionados 99 pacientes con agorafobia. Ambos grupos de tratamiento combinado recibieron 11 sesiones de terapia cognitivo-conductual y uno de los grupos también fue expuesto a 4 sesiones de tratamiento de realidad virtual. Los tratamientos se aplicaron en sesiones individuales una vez a la semana durante 3 meses.

Resultados. Los tres grupos de tratamiento mostraron mejoras estadísticamente significativas. En algunas de las medidas, los grupos de tratamiento combinado mostraron mayores mejoras y el grupo tratado con la exposición de realidad virtual mostró una mayor capacidad de enfrentar los estímulos fóbicos.

Conclusiones. Los tratamientos que combinaron terapia psicofarmacológica y psicológica mostraron una mayor eficacia. Aunque el uso de las nuevas tecnologías dio lugar a una mejoría mayor, siguen existiendo problemas relacionados con la adherencia al tratamiento.

Palabras Clave: Agorafobia, Tratamientos combinados, Paroxetina, Psicoterapia, Realidad virtual

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INTRODUCTION

Agoraphobia is mainly characterized by disproportionate and disabling embarrassment and/or fear in the face of certain external stimuli (crowds, open spaces, venturing far from home, closed spaces, being alone,...) and internal stimuli (feelings of anxiety-panic)[1]. These feelings lead people with agoraphobia to avoid such stimuli or escape from them[2]. Agoraphobia is a relatively frequent disease with prevalence rates as high as 4-6%[3–5].

There is some consensus that certain psychodrugs, cognitive-behavioral therapy (CBT), and combined treatments are first-choice treatments for agoraphobia. There is currently some consensus to justify combining certain psychodrugs with CBT[6,7], especially, paroxetine[8–10].

As regards psychopharmacological treatments, selective serotonin reuptake inhibitors (SSRIs) are first-choice drugs for the treatment of panic disorders and agoraphobia[3,11–13]. Among SSRIs, fluoxetine, paroxetine and sertraline have shown efficacy, safety, low or no dependence and tolerance[14].

As for psychological treatments, reviews have shown high recovery rates among agoraphobia patients (AP) after CBT, which makes them first-choice psychological treatments, where gradual exposure represents a central element of the therapy[15–19]. The clinical use of virtual reality exposure techniques (VRET) seems to be an efficient exposure technique in the treatment of anxiety disorders[20,21].

Very few research studies on agoraphobia have used virtual reality (VR) as an exposure technique, and specific data are not conclusive, Some studies[22] found that traditional CBT with in vivo exposure led to better results than VRET. Other studies found that VRET was able to yield similar (or better) results than CBT, especially when combined with in vivo exposure[23,24]. This combination was found to obtain better results than VRET alone.

Despite these results, the differential efficacy of VRET compared to CBT and their combined use with psychodrugs in clinical AP samples remains to be established. In that sense, the objective of the present study was to test the differential efficacy of the following three treatments of agoraphobia: a treatment combining paroxetine with cognitive-behavioral therapy including VR exposure; a treatment combining paroxetine with traditional cognitive-behavioral therapy; and a treatment using paroxetine only.

The study described below was performed in Spain in accordance with the Good Clinical Practice guidelines and the Helsinki Declaration. The clinical protocol was authorized by the Ethics Committee of the University Hospital of the Canary Islands (Spain), and patients gave their written informed consent before participating in the study.

METHODOLOGY

Patients

The sample was composed of 99 agoraphobia patients. Most of them (n=66) had agoraphobia with panic disorder (F 40.01), mostly female (n=70), with a mean age of 39 years. Evolution time of symptoms ranged from 1 to 30 years, with mean evolution of 8.97 years (SD=6.1). Most patients were chronic (n=66). Inclusion criteria were the criteria of the ICD-10[25] for the diagnosis of agoraphobia (with/without panic disorder). Patients with psychotic symptoms or bipolar disorders, high suicide risk, heart disease, neurological disease or ophthalmologic disease were excluded from the study.

The APs were referred from the regional community mental health services of the Island of Tenerife to an outpatient unit of the University Hospital of Canarias (HUC). Once the diagnosis was corroborated, patients were assessed by a psychiatrist, who prescribed the dose of paroxetine. Psychological treatment started about a month after the paroxetine treatment had begun.

The sample was divided into the following groups: combined treatment involving paroxetine and cognitive-behavioral therapy (PX-CBT, n=27); combined treatment involving paroxetine and cognitive-behavioral therapy, including exposure to virtual reality (PX-CBT-VRET, n=27); and a monotherapy group treated only with paroxetine (PX, n=32).

Instruments and devices

Software and hardware

Virtual environments. Seven local virtual environments were developed: a square and street, an airport building and plane, a bank office, an elevator and underground car park, a beach, a highway, and a cableway. These environments were designed with C ++ and based on OpenGL and a Torque graphics engine. Figure 1 shows pictures of each environment.

Nvidia Quadro FX 3000O was used as graphic support due to the need to move among large spaces and textures in a realistic way. A projection system formed by two video-projectors (F1Design, 3000 lumens and 1024x768 resolution) was also used. The patient uses glasses with polarized filters to produce a 3D effect. The image is projected onto a special screen, with a surface of 2.5 x 2 m.

The patient has a wireless joystick to move around the virtual environments. Likewise, there is a DTS 7.1 audio system installed with 7 loudspeakers and a subwoofer to generate 3D (surround) sound. The systems are controlled by an Intel PIV computer.

Clinical assessment

To verify the diagnosis of agoraphobia in the patients of the HUC psychiatric unit, two instruments were used:

- The *Composite International Diagnostic Interview* (CIDI, 2.1)[26]. The CIDI-2.1 was designed by the World Health Organization. It is a structured interview for major mental disorders, according to the ICD-10 criteria[25]. It estimates both lifetime and 12-month prevalence of mental disorders. The CIDI was adapted to include only questions and criteria related to agoraphobia.
- *Agoraphobia Questionnaire* (AGPH)[27]. This questionnaire measures the general level of agoraphobia with 69 items in a Likert scale. The items assess manifest behavior (alone or with other people), cognitions and psycho-physiological reactions related to agoraphobic situations (alone or with other people). The authors described appropriate psychometric properties for severity of agoraphobia. High test-retest reliability (r=0.69). Internal consistencies were as follows: α=0.93 (overt behavior subscale), 0.94 (physiological responses subscale), and 0.87 (cognitive subscale).

As outcome measures, the following instruments were used:

- *Agoraphobic Cognitions Questionnaire* (ACQ)[28]. The ACQ assesses catastrophic thoughts about both the physical and social consequences of a panic attack. It contains 14 items. Response choice ranges from 1 (I never think this) to 5 (always). The authors have reported a final adequate internal consistency (α=0.80), high test-retest stability (r=0.86). The Spanish translation of this scale was used[29].

a. Plaza de España (Tenerife) environment

b. Tenerife North Airport environment

c. Bank office environment

d. Plaza Weyler underground car park (Tenerife) environment

e. La Tejita beach (Tenerife) environment

f. Tenerife main highway environment

g. El Teide cableway (Tenerife) environment

Figure 1 | *Virtual environments*

- *Body Sensations Questionnaire* (BSQ)[28]. This is a 17-item questionnaire related to physical and physiological body responses. Respondents are asked about the level of fear that these sensations elicit in them on a five-point scale: 1 (not worried) to 5 (extremely frightened). Chambless et al.[28] reported a high internal consistency (α=0.88), and temporal stability (r=0.67). Again, the Spanish translation of the BSQ was used[29].
- *Beck Anxiety Inventory* (BAI)[30], Spanish adaptation[31]. This is a self-administered inventory to assess the general level of anxiety. Its 21 items reflect physiological reactions, somatic complaints and cognitions about anxiety attacks. The scale is responded to on a four-point scale (from not at all to severely). Spanish adaptation reported a high internal consistency (α=0.93). Magán et al.[32] reported an adequate discriminant validity between normal and pathological anxiety.
- *Beck Depression Inventory-II* (BDI-II)[33], Spanish adaptation[34]. This is the second version of a 21-item inventory developed to assess depression severity. Internal consistency estimate for the BDI-II was high (coefficient alpha of 0.89).
- *Subjective Units of Anxiety* (SUA). The phobic environments were rated on a ten-point scale from 0 (no anxiety) to 10 (maximum level of anxiety). These measurements were taken at the end of treatment sessions where patients were exposed to phobic stimuli (in-vivo or VR). Consequently, data are obtained as from session four, when patients began their exposure.
- *Behavioral Avoidance Test*. At the end of the program, patients in both exposure groups (PX-CBT and PX-CBT-VRET) were encouraged to cope with two real scenarios similar to the virtual environments entitled 'square and street' and 'an elevator and underground car park'. Patients were accompanied to these real stimuli by a therapist helper and asked to walk and remain there for a maximum of 20 minutes. They were informed that if they felt anxious, they could return to where the helper was waiting (they could also refuse to carry out the task).

Design

A randomly controlled trial was used. Patients were assigned to any of the three treatment groups (PX-CBT, PX-CBT-VRET, and PX) according to a random computer-generated sequence. Consecutive numbers were assigned to patients when they accepted to participate.

The groups were assessed at pre-treatment (PRE), post-treatment (POST), and 6-month follow-up (FOLOW-UP 6). The PX control group only had measures in the time equivalent to the PRE and POST stages. Then, for ethical reasons, free psychological treatment was provided to those patients who requested it.

Interventions

Both PX-CBT and PX-CBT-VRET groups underwent the same number of sessions: eleven 35-45-minute (weekly) sessions of cognitive-behavioral psychotherapy. The PX-CBT-VRET group also underwent four 12-15 minute VR exposure, as part of exposure sessions. The first 3 sessions were similar in both conditions and were composed of one psychoeducational session on agoraphobia and two training sessions on cognitive restructuring. From sessions 4 to 11, APs were motivated to gradually face phobic stimuli with the help of the cognitive restructuring techniques. The PX group remained on the waiting list for an equivalent time to the duration of psychotherapy in the other two treatment groups (11 weeks).

The psychopharmacological treatment was paroxetine, at a mean dose of 22.60 mg/day. The dose was kept stable during the therapeutic process. Reductions in psychopharmacological treatment were decided following clinical criteria (pregnancies, appearance of undesirable side effects such as galactorrhea or others) and coded.

Statistical analyses

To compare the efficacy of treatments, several MANOVAs were performed for the various outcome measures at the three times assessed (PRE, POST and 6-month follow-up). Between-group comparisons were performed using the Bonferroni method.

RESULTS AND DISCUSSION

First, the characteristics of patients who dropped out of the study at any point in the two experimental groups were assessed. Seven patients in the PX-CBT group and 8 in the PX-CBT-VRET group dropped out; Chi square analysis were performed. No differences were found in drop rates by treatment groups (X^2_1=1.86). Also no significant differences were found according to sex (X^2_1=2.79) or diagnosis (agoraphobia with or without panic disorder, X^2_1=1.39).

Table 1 summarizes the descriptive data of the dependent variables analyzed at each clinical stage.

Once satisfied that the outcome variables were not distributed abnormally, the possible differences between the treatment groups and the control PX group were first compared by performing a pre-post repeated measure analysis of variance (MANOVA). Table 2 summarizes the coefficients obtained and their significance.

As shown in the table 2, all the pre-intervention and post-treatment comparisons were significant in the three groups. Therefore, both combined treatments and the mono-

Table 1 Treatment groups and dependent variables. Means and standard deviations at each stage

Measure	Groups	PRE		POST		FOLLOW-UP 6	
		Mean	SD	Mean	SD	Mean	SD
AGPH	PX+CBT	75.75	28.97	43.50	23.86	44.60	37.83
	PX+CBT+VRET	84.32	25.33	49.59	30.15	39.00	25.07
	PX	82.57	29.23	69.00	23.60		
ACQ	PX+CBT	32.08	11.05	24.21	7.29	24.25	10.60
	PX+CBT+VRET	34.61	9.24	25.52	7.76	20.68	9.22
	PX	30.63	10.00	29.56	9.63		
BSQ	PX+CBT	50.17	13.90	39.17	10.72	40.32	14.94
	PX+CBT+VRET	51.87	14.47	36.22	13.12	34.26	12.49
	PX	54.72	14.47	49.06	13.29		
BAI	PX+CBT	26.75	14.20	11.71	9.08	12.16	9.34
	PX+CBT+VRET	2657	15.53	11.87	10.85	12.84	11.70
	PX	30.44	12.64	22.10	11.43		
BDI-II	PX+CBT	21.96	12.91	12.72	10.60	13.55	11.12
	PX+CBT+VRET	21.43	14.27	12.10	8.97	9.94	9.78
	PX	22.69	11.37	20.03	13.63		

AGPH: Agoraphobia Questionnaire; ACQ: Agoraphobic Cognitions Questionnaire ; BSQ: Body Sensations Questionnaire; BAI: Beck Anxiety Inventory; BDI-II: Beck Depression Inventory-II; PX: Paroxetine; CBT: Cognitive-Behavioral Therapy; VRET: Virtual Reality Exposure Therapy.

therapy treatment improved the adjustment levels of agoraphobia patients. Initially, all three treatments were efficient in reducing agoraphobia symptoms.

The differential efficacy of the treatments reached significance in the decrease of levels of general anxiety (BAI), agoraphobia (AGPH), psychophysiological symptoms (BSQ) and level of depression (BDI-II). The Bonferroni comparison showed that these differences were favorable to the PX-CBT group and PX-CBT-VRET group, when compared with PX group. Effect sizes (η^2) were high, but only for pre-post contrasts. The rest of effects were medium (especially for treatment modalities). These data point out that combined treatments attained better results than monotherapy (only paroxetine).

A second group of analyses was performed to compare the results obtained between the combined treatment groups at follow-up. Again, a repeated measure MANOVA was carried out. Evolution time was introduced as a co-variable because some data suggested[23] that treatment efficacy may be affected by the duration of the disorder. Table 3 summarizes the results obtained.

In this case, all the significant differences found show that both groups improved with time, and no significant differences or interactive effects were found between them in the course of time. In this case, effect size decreased and became low to moderate.

A last group of analyses was performed to assess contextual variables: SUA and BAT. Now, only patients of the two exposure groups (PX-CBT and PX-CBT-VRET) were assessed.

As regards the SUA measures, the global assessments of anxiety experienced from session 4 to 6-month follow-up were taken. Results showed a significant decrease in anxiety experienced as the sessions unfolded ($F_{1.35}$=109.88, p=0.001; η^2=0.74). Figure 2 shows this evolution.

No significant differences were found between both treatment groups, except at follow-up, when the PX-CBT-VRET group reported a slightly lower anxiety level ($F_{1.30}$=3.78; p=0.03; η^2=0.1) to phobic stimuli (M=2.00; SD=1.4) than the PX-CBT group (M=3.20; SD=2.18).

As regards behavioral avoidance tests (BATs), patients were asked to face the real stimuli of walking along a street and a square and enter the elevator and the car park. Four patients in the PX-CBT group and three patients in the PX-CBT-VRET group avoided participating.

Table 2 Pre-post MANOVA in the three treatment groups and the self-reported scales

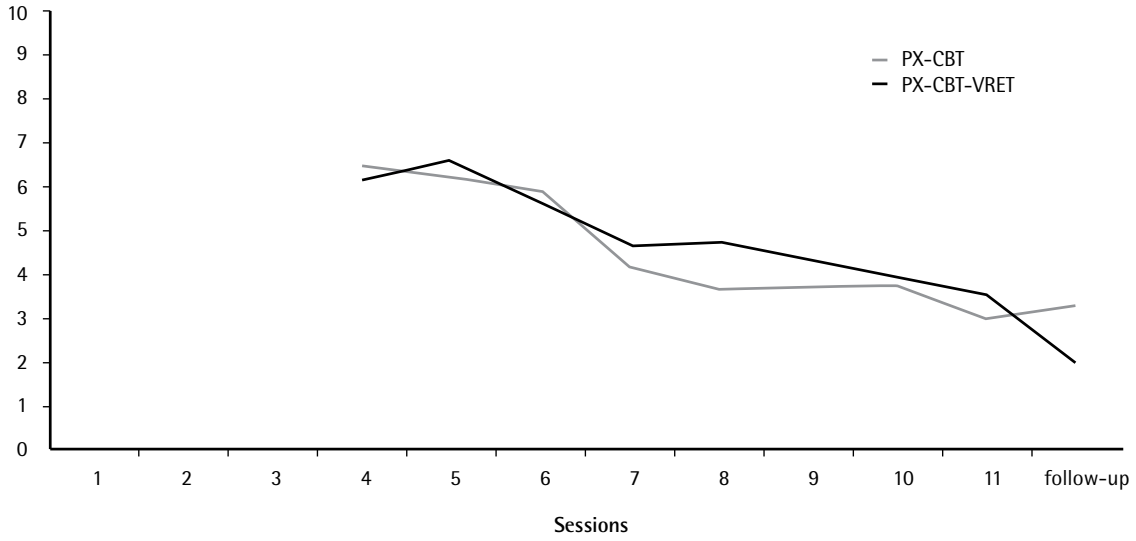
Measure	Source of variation	df	F	P	η^2
AGPH	Pre-post	1, 75	91.424	0.001	0.549
	Treatment	2, 75	3.162	0.048	0.078
	Interaction	2, 75	6.276	0.003	0.143
ACQ	Pre-post	1, 76	48.362	0.001	0.389
	Treatment	2, 76	0.432	0.651	0.011
	Interaction	2, 76	9.195	0.001	0.195
BSQ	Pre-post	1, 76	51.114	0.001	0.402
	Treatment	2, 76	3.964	0.023	0.094
	Interaction	2, 76	3.875	0.025	0.093
BAI	Pre-post	1, 76	103.813	0.001	0.577
	Treatment	2, 76	3.802	0.027	0.091
	Interaction	2, 76	3.386	0.039	0.082
BDI-II	Pre-post	1, 73	44.770	0.001	0.380
	Treatment	2, 73	1.354	0.265	0.036
	Interaction	2, 73	4.940	0.010	0.119

AGPH: Agoraphobia Questionnaire; ACQ: Agoraphobic Cognitions Questionnaire ; BSQ: Body Sensations Questionnaire; BAI: Beck Anxiety Inventory; BDI-II: Beck Depression Inventory-II.

Table 3 Pre-post-follow-up MANOVA of both combined treatment groups in the self-reported measures

Measure	Source of variation	df	F	P	η^2
AGPH	Pre-post-follow-up	1, 35	22.186	0.001	0.388
	Treatment	1, 35	0.292	0.593	0.008
	Interaction	1, 35	0.459	0.503	0.013
ACQ	Pre-post-follow-up	1, 36	10.226	0.003	0.221
	Treatment	1, 36	0.005	0.945	0.000
	Interaction	1, 36	1.843	0.183	0.049
BSQ	Pre-post-follow-up	1, 35	16.551	0.001	0.321
	Treatment	1, 35	0.995	0.325	0.028
	Interaction	1, 35	2.161	0.151	0.058
BAI	Pre-post-follow-up	1, 35	22.944	0.001	0.396
	Treatment	1, 35	0.032	0.860	0.001
	Interaction	1, 35	0.097	0.757	0.003
BDI-II	Pre-post-follow-up	1, 35	13.732	0.001	0.282
	Treatment	1, 35	0.174	0.679	0.005
	Interaction	1, 35	0.319	0.576	0.009

AGPH: Agoraphobia Questionnaire; ACQ: Agoraphobic Cognitions Questionnaire; BSQ: Body Sensations Questionnaire; BAI: Beck Anxiety Inventory; BDI-II: Beck Depression Inventory-II.



Because SUAs were only taken when patients began to expose, data begin in session four. Also, because PX patient control group was not exposed to phobic stimuli, no data are provided for them.

Figure 2 | *Level of subjective anxiety units (SUA), in sessions and follow-up, for the two combined treatment groups*

In the street and square scenario, the PX-CBT-VRET group stayed significantly longer ($F_{1.30}$=6.03; p=0.02; η^2=0.18) in minutes (M=15.67; SD=3.2) than the PX-CBT group (M=12.33; SD=4.17). No differences were found ($F_{1.30}$=2.56) in the level of anxiety experienced by both groups (PX-CBT group: M=3.73; SD=2.15; PX-CBT-VRET group: M=2.54; SD=1.94).

In the elevator and car park scenario, again, the PX-CBT-VRET group ($F_{1.30}$=3.9; p=0.05; η^2=0.12) stayed slightly longer (M=15.00; SD=2.67) than the PX-CBT group (M=12.67; SD=3.724). Like in the previous scenario, no differences were found ($F_{1.30}$=0.02) in the anxiety level experienced by both groups (PX-CBT group: M=2.23; SD=2.24; PX-CBT-VRET group: M=2.2; SD=1.78).

Pharmacological changes were appraised by the psychiatric service from the end of treatment until the 6-month follow-up. Of the 20 patients assessed in the PX-CBT group, 10 (50%) had begun to decrease the dose of paroxetine or discontinue its use. In the PX-CBT-VRET group, 19 patients were assessed. In this group, the proportion of patients quitting paroxetine was higher: 15 patients (78.9%) had begun to discontinue the medication.

CONCLUSIONS

The first conclusion is related to general efficacy of the three treatment groups: both combined psychological treatment/psychodrug groups and paroxetine groups diminished the agoraphobia symptoms. Also, agoraphobia patients receiving combined treatments improved significantly more than those treated only with psychodrugs (paroxetine). But doubts still remain about the greater efficacy of using VR compared to traditional psychological treatments. In addition, when treatment efficacy was measured immediately after treatment, combined treatment with PX-CBT seemed to yield better results (greater symptom decrease) than the PX-CBT-VRET combination, at least in general measures of anxiety and agoraphobia. Moreover, the PX-CBT-VRET treatment was not proven to generate greater adherence to treatment, since dropout level was similar in this group and the PX-CBT group.

However, an analysis of discontinuation of the drug, BAT tests, and follow-up results revealed a slightly greater efficacy of the group treated with PX-CBT-VRET than the PX-CBT group.

With these data in mind, we can consider that the use of the VRET procedure with agoraphobia patients can imply an improvement in well-established treatments (both psychological and psychiatric). But doubts still remain whether those improvements imply a significant increment in the health of patients. Also, the drop-out rate, added to the rate of patients who refused to confront phobic stimuli (as BAT procedure), reveal that there remain a significant number of patients for whom even VRET procedures fail to motivate them to change.

Some questions remain unanswered: (i) it is complicated to determine which stimuli are really phobic for each person with agoraphobia. Although seven scenarios were prepared

with local references that provided greater ecological validity, there is no guarantee that they are the best scenarios. (ii) Paroxetine was the drug used in all cases. Differential efficacy in groups not treated with psychodrugs remains to be determined. In addition, dual drugs[9,24] are showing high efficacy in the treatment of anxiety and phobias. Their use should be compared in combined treatments with psychological therapies. (iii) No insight was provided on differential efficacy as a function of the evolution of the disorder. Patients treated were referred by mental health facilities without considering chronicity and randomly assigned to the different treatment groups. Differential efficacy depending on the acute or chronic nature of agoraphobia also remains to be determined.

Finally, the data shown here support a greater efficacy of combined interventions compared to psychopharmacological monotherapies in the treatment of agoraphobia. The slight gain of combined treatments using VRET does not allow us to state its superiority. In this sense, therapists must be careful in their recommendation, because new data are needed to confirm differential efficacy.

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