Research Article

VIRTUAL REALITY EXPOSURE THERAPY IN ANXIETY DISORDERS: A QUANTITATIVE META-ANALYSIS

David Opriş,[1]* Sebastian Pintea,[1] Azucena García-Palacios,[2] Cristina Botella,[2] Ştefan Szamosközi,[3] and Daniel David[1,4]

Virtual reality exposure therapy (VRET) is a promising intervention for the treatment of the anxiety disorders. The main objective of this meta-analysis is to compare the efficacy of VRET, used in a behavioral or cognitive-behavioral framework, with that of the classical evidence-based treatments, in anxiety disorders. A comprehensive search of the literature identified 23 studies (n = 608) that were included in the final analysis. The results show that in the case of anxiety disorders, (1) VRET does far better than the waitlist control; (2) the post-treatment results show similar efficacy between the behavioral and the cognitive behavioral interventions incorporating a virtual reality exposure component and the classical evidence-based interventions, with no virtual reality exposure component; (3) VRET has a powerful real-life impact, similar to that of the classical evidence-based treatments; (4) VRET has a good stability of results over time, similar to that of the classical evidence-based treatments; (5) there is a dose–response relationship for VRET; and (6) there is no difference in the dropout rate between the virtual reality exposure and the in vivo exposure. Implications are discussed. Depression and Anxiety 29:85–93, 2012.

Key words: *treatment efficacy; waiting list; evidence-based practice; long-term effect; randomized controlled trial; behavior therapy; cognitive behavior therapy*

INTRODUCTION

According to recent estimates on the US population, the current 12-month prevalence for the anxiety disorders is 18.1%,[1] whereas in Europe a 13.6% lifetime history of any anxiety disorder was found.[2] These figures make anxiety disorders a very important area for mental health research.

The evidence-based interventions movement has shown that cognitive behavior therapy (CBT) is one of the best-validated treatments for anxiety disorders.[3] For example, exposure-based treatments (a particular form of CBT) are proving to be very successful for treating anxiety disorders and they are among the most effective evidence-based interventions for these disorders.[4–6]

[1]Department of Clinical Psychology and Psychotherapy, Babeş-Bolyai University, Cluj-Napoca
[2]Department of Basic and Clinical Psychology and Psychobiology, Jaume I University, Castellón de la Plana
[3]Department of Applied Psychology, Babeş-Bolyai University, Cluj-Napoca
[4]Department of Oncological Sciences, Mount Sinai School of Medicine, New York

The authors disclose the following financial relationships within the past 3 years: Contract grant sponsor: Ministerio de Ciencia e Innovacion, Spain; Contract grant number: PSI2010-17563.

*Correspondence to: David Opriş, Department of Clinical Psychology and Psychotherapy, Babeş-Bolyai University, No. 37, Republicii Street 400015, Cluj-Napoca, Romania.
E-mail: david.opris@ubbcluj.ro

Received for publication 18 July 2011; Revised 19 September 2011; Accepted 25 September 2011

DOI 10.1002/da.20910
Published online in Wiley Online Library (wileyonlinelibrary.com).

Authors contribution: David Opriş—design of the study, data interpretation and analysis, writing the manuscript; Sebastian Pintea—data interpretation and analysis; Azucena García-Palacios—data interpretation and analysis; Cristina Botella—design of the study, data interpretation and analysis; Ştefan Szamosközi—data interpretation; Daniel David—design of the study, data interpretation.

Virtual reality exposure therapy (VRET) is a new tool for conducting exposure therapy with the help of a computer-generated virtual environment, allowing for the systematic exposure to the feared stimuli within a contextually relevant setting.[7] It is important to point out that the generalization of the VRET's results to the patient's real life is the ultimate measure for the success of this treatment form.[8]

A recent meta-analysis of randomized clinical trials (RCT) comparing VRET with in vivo exposure and with control conditions[9] followed rigorous methodological criteria, analyzing only well-controlled clinical trials with random or matched assignment, with at least one VRET condition, and including an active or inactive control group. In this meta-analysis, VRET was investigated as a stand-alone treatment, leading to the exclusion of all studies combining VRET with CBT in the treatment condition. The exclusion criteria were as follows: within or cross-over design, studies including cognitive interventions, imaginal exposure intervention in the control group, and lack of data to compute effect sizes. As a result, 13 studies ($n = 397$) were included. The results showed a large mean effect size for VRET compared to the control conditions with regard to the primary outcome measure (domain-specific subjective distress), with Cohen's $d = 1.11$ (SE = .15, 95% CI [0.82–1.39]). Large effect sizes were found when the analyses were run separately for each disorder. This result was also found in regard with the secondary outcome variables: general subjective distress, cognition, behavior, and psychophysiology. Compared to in vivo exposure, VRET was shown to be equally effective, even having a small advantage over in vivo exposure (Cohen's $d = 0.35$, SE = .15, 95% CI [0.05–0.65]). Unfortunately, the small number of studies and the fact that most were about phobias treatments does not allow the generalization of these results to all the anxiety disorders. Also, the authors were able to show a trend for a dose–response relationship for VRET, but the results did not reach statistical significance.

A recent systematic review, reporting controlled trials selected using strict methodological criteria, gave us an overview of the efficacy of VRET in anxiety disorders.[8] They identified 20 articles on this subject, noting that often the treatment protocols included multiple components, with some of the components not being the state-of-the art treatments for those specific disorders. Also, the separate contribution of the virtual reality exposure was impossible to determine, because it was combined with other techniques. This study gave us a more sobering look at the outcomes of the VRET interventions in anxiety disorders, stating that only in the case of fear of flying and acrophobia there are enough data available to conclude that VRET is effective. At the same time, they emphasized that the first results are promising in the case of more complex anxiety disorders, such as panic disorder and social phobia. Another observation of the authors was that the effect of the VRET on the behavioral measures points toward a very good generalization of the results to the real world. However, because this study was a systematic review it did not report global effect sizes.

Until now, for the anxiety disorders, there has been no meta-analysis in which the treatments combining a virtual reality exposure component with classical evidence-based interventions (e.g. cognitive-behavioral therapy and virtual reality, or behavioral therapy and virtual reality) were directly compared with the classical evidence-based interventions (in which no virtual reality component was used). In our opinion, this kind of analysis is very important for the future development of virtual reality psychotherapy, given the fact that the evidence-based treatments are the golden standard interventions, and hence the aim of this article is to perform this analysis.

Concerning the classical evidence-based treatments for the anxiety disorders, the Society of Clinical Psychology, Division 12 of American Psychological Association, has compiled a list of evidence-based treatments for the different disorders.[10] The treatments that have strong research support and are also uncontroversial are for panic disorder—cognitive-behavioral therapy; for specific phobias—exposure therapies; for social phobia and public speaking anxiety—cognitive-behavioral therapy; for post-traumatic stress disorder—prolonged exposure and cognitive processing therapy; for generalized anxiety disorder—cognitive-behavioral therapy. In the following discussions, by classical evidence-based treatments we mean the treatments mentioned above. It is worth noting that for the anxiety disorders all nonpharmacological treatments that have strong research support and are also uncontroversial there are either behavioral therapies or cognitive-behavioral therapies.

The current review will focus on how effective the virtual reality exposure enhanced evidence-based interventions are compared to the classical evidence-based interventions, and not on how effective the virtual reality exposure is in itself.

The studies presented in the theoretical introduction of this article used the VRET acronym for the stand-alone interventions involving in virtuo exposure, in a behavioral paradigm. In this article, VRET is defined as a treatment that includes a virtual reality component, either in the behavioral framework (i.e. behavioral therapy+VR exposure) or in the cognitive-behavioral framework (i.e. cognitive-behavioral therapy+VR exposure).

The main novelty this meta-analysis brings is the comparison of VRET interventions with the classical evidence-based interventions (i.e. either cognitive-behavioral therapy with no VR exposure, or behavioral therapy with no VR exposure), employing data from RCTs. It is also the first meta-analysis to report data regarding the impact of VRET on the real-life and the long-term effects of VRET.

The present study will also address whether VRET shows a dose–response relationship.

Concerning the dropout rate, we will analyze whether there is a difference between the virtual reality exposure and the in vivo exposure.

OBJECTIVES

The present meta-analysis tries to provide answers to the following questions: (1) what is the efficacy of VRET compared to waitlist?; (2) what is the efficacy of VRET compared to classical evidence-based interventions?; (3) what is the impact of VRET on the real life, or in other words to what extent do the results of the treatment generalize to real-life situations for the clients?; (4) what are the long-term effects of VRET?; (5) is there a dose–response relationship for VRET?; (6) is there a difference in the dropout rate between the virtual reality exposure and the in vivo exposure?

METHODS

STUDY SELECTION

We selected RCTs of VRET in anxiety disorders using the search strategy described below. The search has been conducted on December 4, 2010. We searched the following databases: PsycINFO, PubMed, ISI Web of Science, and Academic Search Premier. We used the following search terms: "VRET," "virtual reality and anxiety," "virtual reality and exposure," "virtual reality and phobia," "virtual reality and panic disorder," "virtual reality and generalized anxiety disorder," "virtual reality and obsessive compulsive disorder," and "virtual reality and posttraumatic stress disorder." We also searched the references from the recent randomized control trials, meta-analysis, and systematic reviews on the topic.

The inclusion criteria were randomized allocation of the subjects in the experimental conditions; studies with human subjects; studies regarding the efficacy of VRET in anxiety disorders; the existence of at least one VRET condition and one control condition (classical evidence-based intervention or waitlist); studies reporting original empirical findings; studies published in peer-reviewed journals; and studies written in English. The exclusion criteria were as follows: not enough data to calculate the effect sizes; nonclinical population; case studies; book chapters; dissertations; and less than 10 participants in the VRET group. This cut-off point was chosen because it was also used in Meyerbröker and Emmelkamp's systematic review,[8] and by using previous criteria we ensure the systematic extending of knowledge.

The algorithm and the results of the study search and selection are detailed in the PRISMA Flow Diagram[11] shown in Figure 1. On the basis of this standardized methodology, in the meta-analysis we included 21 articles reporting 23 studies, with a total sample size of 608 participants. From these, three articles were reporting only follow-up data.[12–14]

PROCEDURE

We collected data regarding the following variables: disorder, treatment condition (behavioral therapy augmented by virtual reality exposure, or cognitive-behavioral therapy augmented by virtual reality exposure), comparison condition (in vivo exposure, CBT, imaginal exposure, group CBT or a combination of them, and waitlist) and the number of participants per condition (Table 1).

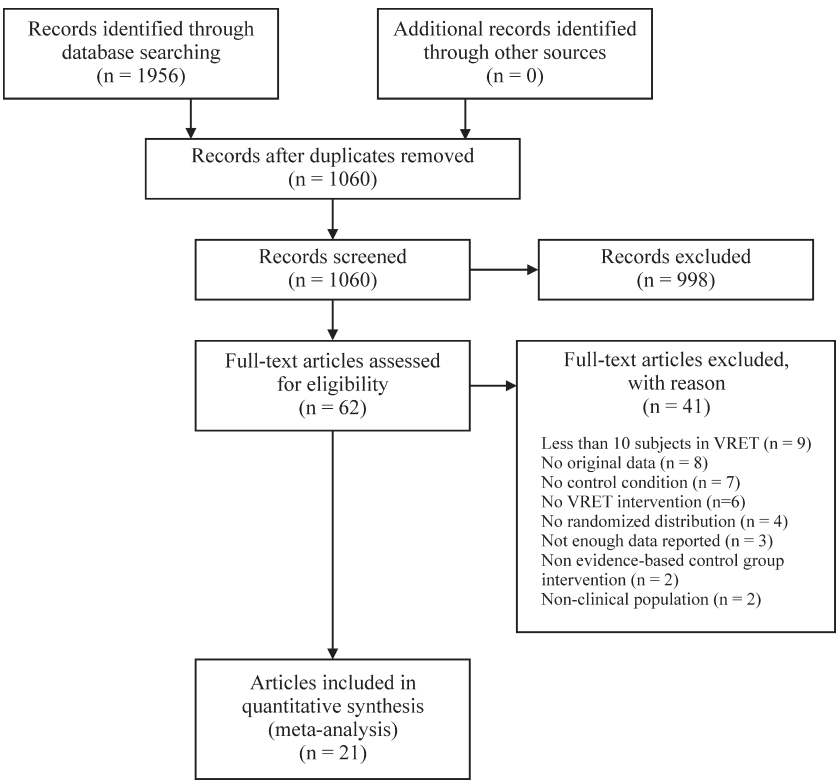

Figure 1. PRISMA flow chart.

TABLE 1. Studies included in the meta-analysis and post-treatment primary outcome effect sizes

Study	Disorder	Treatment group	Comparison group	*N*	Post-treatment primary outcome effect sizes: Cohen's *d*	Post-treatment primary outcome effect sizes: No. of effect sizes per study
Rothbaum et al.[23]	Fear of flying	VRE+CBT	IVE+CBT	30	0.1	2
Rothbaum et al.[23]	Fear of flying	VRE+CBT	WL	30	0.64	2
Wiederhold et al.[30]	Fear of flying	VRE+BT	IMEx	30	0.46	2
Mühlberger et al.[32]	Fear of flying	VRE+CBT	CBT	37	1.28	2
Rothbaum et al.[24]	Fear of flying	VRE+CBT	IVE+CBT	54	−0.06	2
Rothbaum et al.[24]	Fear of flying	VRE+CBT	WL	54	0.47	2
Krijn et al.[31]	Fear of flying	VRE+BT	CBT	45	0.41	2
Choi et al.[16]	Panic disorder/agoraphobia	VRE+CBT	IVE+CBT	40	−0.45	4
Botella et al.[18]	Panic disorder/agoraphobia	VRE+CBT	IVE+CBT	24	−0.16	4
Botella et al.[18]	Panic disorder/agoraphobia	VRE+CBT	WL	25	1.74	4
Peñate et al.[33]	Panic disorder/agoraphobia	VRE+CBT	IVE+CBT	28	0.33	2
Pitti et al.[34]	Panic disorder/agoraphobia	VRE+CBT	IVE+CBT	27	0.15	2
Klinger et al.[35]	Social phobia	VRE+CBT	IVE+GrCBT	36	−0.18	1
Wallach et al.[25]	Social phobia	VRE+CBT	IMEx+CBT	58	0.34	3
Wallach et al.[25]	Social phobia	VRE+CBT	WL	58	0.85	3
Robillard et al.[26]	Social phobia	VRE+CBT	IVE+CBT	30	0.12	4
Robillard et al.[26]	Social phobia	VRE+CBT	WL	29	1.34	4
García-Palacios et al.[27]	Arachnophobia	VRE+BT	WL	23	2.38	1
Michaliszyn et al.[36]	Arachnophobia	VRE+CBT	IVE+CBT	32	−0.26	2
St-Jacques et al.[37]	Arachnophobia	VRE+CBT	IVE+CBT	31	0.01	2
Emmelkamp et al.[38]	Acrophobia	VRE+BT	IVE	33	0.24	2
Krijn et al.[28]	Acrophobia	VRE+BT	WL	28	1.11	2
Difede et al.[29]	PTSD	VRE+BT	WL	21	1.82	1

Note: VRE+BT, behavioral therapy augmented by virtual reality exposure; VRE+CBT, cognitive-behavioral therapy augmented by virtual reality exposure; CBT, cognitive-behavioral therapy; IVE, in vivo exposure; WL, wait list; IMEX, imaginal exposure; GrCBT, group cognitive-behavioral therapy; PTSD, post traumatic stress disorder. Definition of categories for Cohen's *d*: no effect (0–0.2), low effect (0.2–0.5), medium effect (0.5–0.8), and large effect (>0.8). The number of effect sizes refers to the effect sizes taken into account at the primary outcomes calculations.

The dependent variables were classified as follows: primary outcomes (the main outcomes used to determine the effects of the interventions), and real-life impact outcomes (behavioral approach test [BAT], behavioral approach, actual flights, and clinical improvement).

The comparison conditions to which VRET was compared were categorized as follows: (1) classical evidence-based interventions; and (2) waitlist.

Primary outcomes are the main outcomes used to determine the effects of the interventions. Usually, they include the behavioral measurements, but owing to the fact that we separately computed the real life impact outcomes we decided to exclude the behavioral measurements from the primary outcomes. Patients' subjective ratings and clinician-administered interviews listed in Table 2 served as the primary outcome measures.

The real-life impact of the VRET treatments is estimated from behavioral measures (BAT, behavioral approach, and actual flights) and from clinical improvement measures in the case of panic disorder.

Regarding the effects of VRET on the behavioral measures, we know that in the anxiety disorders, beyond the subjective level measures of distress, a very important aspect is the functional impairment owing to the behavioral incapacity of the subject to fulfill the relevant tasks for his daily living.[15] It was also pointed out by Powers and Emmelkamp's earlier meta-analysis on VRET[9] that analyzing the behavioral measures would provide data about the generalization of the treatment's results to the situations from the patient's real life. As most of the recent clinical trials included this kind of measures, we were able to calculate the effect sizes of the VRET compared to the classical evidence-based treatments on the behavioral measures.

But the effects of the treatment on the real life can also be assessed by the measures of clinical improvement. For example, in the case of two studies on panic disorder with or without agoraphobia, the authors did not include a behavioral measure but they measured the clinical improvement. The first study[16] used a composite measure of high end-state functioning, combining a reduction to zero of the panic attacks over a period of 4 weeks with a score of 2 or less on the 9-point Clinician's Severity Rating of Anxiety Disorder Interview Schedule—Revised.[17] The second study[18] considered being free of panic or present a 50% reduction in the panic frequency as a criteria of clinical improvement.[19] We believe that this measure of clinical improvement is also an appropriate way of estimating the effects of the treatment on the patient's real life.

EFFECT SIZE CALCULATION

We calculated Cohen's *d* effect sizes, according to the published procedures.[20] We calculated all the effect sizes using the means and *SD*s, given that these data were available. When means and *SD*s were not available, we calculated the effect sizes using a specialized computer program, The Meta-Analysis Calculator, available freely on Internet.[21] The Cohen's *d* effect sizes were categorized as no effect (0–.2), small effect (.2–.5), medium effect (0.5–0.8), and large effect (>0.8).[22] When there were more outcomes, for example when calculating the global score from all the outcomes reported in a study, the outcomes were combined according to Hunter and Schmidt.[20] For the effect size of all the studies, we used the random effects model, due to the heterogeneity of the studies. To avoid the bias induced by the differences in the sample sizes of the studies, we chose

TABLE 2. Primary outcomes for each anxiety disorder

Disorder	Primary outcomes
Fear of flying	Fear of flying inventory (FFI), questionnaire on attitudes toward flying (QAF), fear of flying scale (FFS), general fear of flying questionnaire (GFFQ), flight anxiety situations questionnaire (FAS), flight anxiety modality questionnaire (FAM)
Panic disorder/ agoraphobia	Anxiety sensitivity index (ASI), panic belief questionnaire (PBQ), agoraphobic cognition questionnaire (ACQ), body sensation questionnaire (BSQ), fear and avoidance scales (FAS), panic disorder severity scale (PDSS), agoraphobia subscale of fear questionnaire (FQ Agoraphobia subscale)
Social phobia	Liebowitz social anxiety scale (LSAS), fear of negative evaluation (FNE), self-statements during public speaking (SPSS total), social phobia scale (SPS), appraisal of social concerns (ASC)
Arachnophobia	Fear of spiders questionnaire (FSQ), spider phobia belief questionnaire (SPBQ), spider phobia questionnaire for children (SPQ-C)
Acrophobia	Acrophobia questionnaire (AQ), attitude towards height questionnaire (ATHQ)
PTSD	Clinician administered PTSD scale (CAPS)

PTSD, post-traumatic stress disorder.

to calculate *D* (the average weighted effect size) instead of *d*, and variance of *D* (VAR *D*) instead of SD of *d*.[20]

We computed overall effect sizes in which data from all the disorders are taken together. We also computed separate effect sizes for each disorder, given the fact that at least two studies were available. When there are no data reported for the disorder level of analysis, this is due to the fact that there were not enough studies to calculate an effect size.

RESULTS

VRET VS. WAITLIST

Concerning the comparison of VRET to waitlist control at post-treatment on the primary outcome, there were eight studies.[18,23–29] The results show a large and statistically significant overall effect size ($D = 1.12$; VAR $D = .34$, 95% CI [0.71–1.52], $P < .05$), a large and statistically significant effect size on social phobia (two studies; $D = 1.01$; VAR $D = .05$, 95% CI [0.69–1.33], $P < .05$) and a medium and statistically significant effect size for fear of flying (two studies; $D = .53$; VAR $D = .007$, 95% CI [0.41–0.64], $P < .05$) on the primary outcomes.

VRET VS. CLASSICAL EVIDENCE-BASED INTERVENTIONS

At post-treatment. There were 15 studies regarding the comparison at post-treatment between the VRET and the classical evidence-based treatments at the level of primary outcomes.[16,18,23–26,30–38] The results show no overall effect on the primary outcomes for VRET compared to the classical evidence-based treatments ($D = .16$, VAR $D = .16$, 95% CI [−0.03–0.36], $P > .05$). When the analysis was repeated for each anxiety disorder, the results were similar for panic disorder/agoraphobia (four studies; $D = -.07$, VAR $D = .09$, 95% CI [−0.38–0.23], $P > .05$), social phobia (three studies; $D = .13$, VAR $D = .04$, 95% CI [−0.11–0.38], $P > .05$), and arachnophobia (two studies; $D = -.12$, VAR $D = .01$, 95% CI [−0.31–0.06], $P > .05$). In the case of fear of flying (five studies; $D = .40$, VAR $D = .21$, 95% CI [−0.005–0.81], $P > .05$), a small effect size in favor of the VRET intervention was obtained, but the result was not statistically significant.

There were eight studies regarding the comparison at post-treatment between the VRET and the classical evidence-based treatments at the behavioral level.[23–25,31,33,36–38] The overall effect size of $D = -.03$ (VAR $D = .07$, 95% CI [−0.22–0.14], $P > .05$) revealed no effect for VRET relative to the classical evidence-based treatments. There were enough studies to repeat the analysis for specific disorders only in the case of fear of flying (three studies; $D = -.02$, VAR $D = .02$, 95% CI [−0.19–0.14], $P > .05$) and arachnophobia (two studies; $D = -.27$, VAR $D = .07$, 95% CI [−0.66–0.10], $P > .05$), and the results were the same as for the overall effect at behavioral level.

But the effects of the treatment on the real life can also be assessed by the measures of clinical improvement, and there are two studies on panic disorder with or without agoraphobia measuring the clinical improvement.[16,18] Combining the data from these two studies, we obtained a small but statistically significant effect size, favoring the classical evidence-based treatments over the VRET interventions ($D = -.22$, VAR $D = .02$, 95% CI [−0.43−0.005], $P < .05$).

At follow-up. Regarding the comparison at follow-up between the VRET and the classical evidence-based treatments at the level of primary outcomes, there were seven studies for the 3–6 months follow-up[23,24,31,33,36–38] and three studies for 1-year and beyond follow-up.[18,23,24] For the 3–6 months follow-up the overall primary outcome effect size of $D = -.02$ (VAR $D = .18$, 95% CI [−0.33–0.29], $P > .05$) revealed no effect for VRET relative to the classical evidence-based treatments. For the 1-year and beyond follow-up, the overall primary outcome effect size of $D = -.11$ (VAR $D = .01$, 95% CI [−0.26–0.03], $P > .05$) revealed no effect for VRET relative to the classical evidence-based treatments. When analyses were taken down at the disorder level, all the results were the same: fear of flying at 3–6 months follow-up (three studies; $D = -.02$, VAR $D = .30$, 95% CI [−0.64–0.60], $P > .05$), fear of flying at the 1-year or more follow-up (two studies; $D = -.18$, VAR $D = .001$, 95% CI [−0.23–−0.12], $P < .05$), panic disorder/agoraphobia

at 3 months to 1-year follow-up (two studies; $D = .18$, VAR $D = .004$, 95% CI [0.10–0.26], $P < .05$) and arachnophobia at 3–6 months follow-up (two studies; $D = -.20$, VAR $D = .04$, 95% CI [−0.49–0.08], $P > .05$).

There were four studies regarding the comparison at the 3–6 months follow-up between the VRET and the classical evidence-based treatments at the behavioral level.[23,30,31,36] At the behavioral level, the overall effect size of $D = .24$ (VAR $D = .09$, 95% CI [−0.05–0.53], $P > .05$) revealed no statistically significant effect for VRET relative to the classical evidence-based treatments. Three studies are on fear of flying and in their case there was a small, but statistically significant effect size ($D = .33$; VAR $D = .08$, 95% CI [0.009–0.66], $P < .05$), favoring the VRET interventions.

At the follow-up, we also compared the VRET with the classical evidence-based treatments regarding the clinical improvement in the case of panic disorder.[16,18] The effect size was very small and without statistical significance ($D = -.20$, VAR $D = .02$, 95% CI [−0.50–0.10], $P > .05$).

To test whether there is a dose–response relationship for VRET, we have tested whether there is a linear relationship between the number of sessions and the effect size obtained in each study, using the procedure suggested by Hedges and Olkin.[39] Thus, we performed a weighted linear regression.

For the regression coefficient drawn directly from the output of SPSS, the corrected standard error was calculated by dividing the standard error provided by SPSS with the square root of the mean square error of the model (MSE). The statistical significance of the predictor was calculated using the Z-statistic, following a normal distribution, where the slope was divided by its corrected standard error.

The analysis revealed an unstandardized regression coefficient $B = 1.40$, a standardized coefficient $\beta = .26$ with $Z = 23.48$ significant at $P < .01$. In conclusion, we can confirm the hypothesis that the number of sessions moderates the effect size obtained in the studies.

We performed the analysis regarding the difference in the dropout rate at post-treatment between the virtual reality exposure and the in vivo exposure. Taking into account the studies included in this systematic review, the overall dropout rate in the virtual reality exposure condition was of 16 subjects (from 174 subjects initially recruited) and in the in vivo exposure condition of 20 subjects (from 181 subjects initially recruited). The overall dropout rate showed no difference between the virtual reality exposure and the in vivo exposure, χ^2 $(1, N = 355) = .33$, $P > .05$.

DISCUSSION

The purpose of this meta-analysis was to study the efficacy of the VRET interventions in anxiety disorders. We are not trying to show the contribution of the virtual reality exposure per se, instead we are interested in how well the interventions incorporating a virtual exposure component did compared to the classical evidence-based interventions used in anxiety disorders. As a result, in the following discussion, VRET means either behavioral therapy augmented by virtual reality exposure, or cognitive-behavioral therapy augmented by virtual reality exposure.

Our results show that, in the case of anxiety disorders, (1) VRET does far better than the waitlist control; (2) the post-treatment results show similar efficacy between the behavioral and the cognitive-behavioral interventions incorporating a virtual reality exposure component and the classical evidence-based interventions, with no virtual reality exposure component; (3) VRET has a powerful real-life impact, similar to that of the classical evidence-based treatments; (4) VRET has a good stability of results in time, similar to that of the classical evidence-based treatments; (5) there is a dose–response relationship for VRET; and (6) there is no difference in the dropout rate between the virtual reality exposure and the in vivo exposure.

Concerning the comparison of VRET to waitlist control at post-treatment, on the primary outcome measure, there is a large and statistically significant overall effect size, showing a larger efficacy of the VRET relative to the waitlist. This result is similar to the one in Powers and Emmelkamp's meta-analysis.[9] At the disorder level of analysis, there is a large and statistically significant effect size on social phobia and a medium and statistically significant effect size for fear of flying on the primary outcome measures.

The results show that at post-treatment the VRET and the classical evidence-based interventions have the same efficacy. These results are true for both primary outcome measures and behavioral measures, with a small but statistically significant effect size favoring the classical evidence-based interventions in the case of clinical improvement measures for panic disorder. At the disorder level of analysis, fear of flying, panic disorder with or without agoraphobia, social phobia, and arachnophobia have a similar efficacy on the primary outcome measures. Fear of flying and arachnophobia have a similar efficacy on the real-life impact outcomes.

We have to note here that the prior meta-analysis on the efficacy of behavioral therapy augmented by virtual reality exposure[9] found a superiority of the behavioral therapy augmented by virtual reality exposure over the in vivo exposure. In this study, we found that the efficacy is the same for VRET compared to the classical evidence-based interventions.

Regarding the long-term efficacy of VRET, we calculated the follow-up effect sizes. There was a similar efficacy for VRET and for the classical evidence-based treatments at follow-up on both primary outcomes and real-life impact outcomes (behavioral measures and clinical improvement measures). One exception is the fear of flying, with a small but statistically significant effect size favoring VRET.

Regarding the dose–response relationship, our data show that more sessions of VRET have a larger effect.

These results are arguments for the usefulness of VRET in clinical psychology and in the psychological treatments field and for a wider application of VRET in the clinical practice. Emmelkamp[40] presented a number of advantages that virtual reality exposure has over the traditional exposure: the exposure can be performed inside the therapist's office, a convenient and safe environment in itself; the therapist has better control over the content and the pace of the exposure; the exposure can be repeated as much as needed; the exposure can be customized, to a certain degree, for a particular patient; in the case of fear of flying the virtual reality exposure is also very cost-effective.

Virtual reality exposure can be even more useful for PTSD treatment. In the case of exposure therapy, Foa and Kozak's emotional processing has been proposed as a mechanism of change.[41] The authors state that to change a fear structure (fear-relevant information from the patient's memory), this structure has to be activated first. Following the fear structure's activation, new and corrective information can be incorporated in the memory structure, leading to a change in the fear response.[41] There are some PTSD patients who are unable to access their memories related to the traumatic experiences, and as a result their chances of significant recovery are small.[29] Virtual reality can help these patients to recall the traumatic memories, and in this way facilitate the process of change, by providing a context similar to that in which the traumatic event took place.[29] Also, in the case of terrorist attacks it may be impossible to conduct in vivo exposure, as it is the case with the PTSD related to the September 11th attack on World Trade Center. Here, the early stages of the exposure cannot be performed owing to the fact that the World Trade Center building does not exist anymore. Also, it may be difficult and unsafe to treat combat-related PTSD with in vivo exposure in Iraq. VR exposure can also help to overcome some of the limitations of in vivo exposure. It seems that despite the proven efficacy of in vivo exposure, not all patients benefit from this treatment. And most people with anxiety disorders never seek treatment.[42] Choy et al.[43] found it necessary to analyze the overall effectiveness of in vivo exposure, whereas at the same time they took into account aspects such as treatment motivation and adherence. These authors reported dropout rates ranging from 0 to 45% for in vivo exposure for treating specific phobias in adults. A possible explanation for these high attrition rates is that patients consider it to be too threatening to confront the feared object or situation. VR exposure could help to increase the likelihood of a patient to be willing to start and complete an exposure treatment. There are also studies reporting a high preference for VR exposure when patients are informed about the procedure of in vivo and VR exposure therapy (i.e. [44]).

Our results showed no difference in dropout between the VR exposure and the in vivo exposure conditions. However, there are a few limits regarding this analysis. First, there were only 11 studies comparing VR exposure with in vivo exposure, with one study reporting the dropout rate but failing to specify the exact numbers relative to the treatment conditions. Five studies reported no dropout at all, and most of the remaining studies reported a small and equally distributed among the treatment conditions dropout. Second, a detailed reporting about the causes of the dropout in each condition was not available. A more detailed analysis would have been important since some of the dropouts were not owing to the treatment acceptability for the patients (i.e. scheduling problems, decision by therapist). We suggest that the future studies should include more detailed dropout data that we think will provide valuable information regarding the strengths and weaknesses of each treatment condition. For example, we analyzed the dropout in the virtual reality conditions from all the studies included in this systematic review. Three studies reported the existence of a relatively high number of subjects (a total of 25 subjects) who lacked an emotional reaction to the VR environment and as a result dropped out[28,31] or were moved by the experimenter to the in vivo condition.[36] This shows that not all patients can benefit from the VRET. But, on the other hand, we also know that some patients, who fail to respond to classical evidence-based treatments such as prolonged exposure therapy, do respond well to VRET.[29] Having a similar efficacy with the classical evidence-based interventions and given certain advantages of virtual reality exposure over in vivo exposure, justifies more focus on the VRET regarding both research and clinical practice.

Also, we think it is necessary to compare VRET with other kinds of Internet and Computer Technology-based treatments, such as computer-aided psychotherapy and Internet-based treatments. For example, a recent RCT has shown that VRET, computer-aided exposure with therapist involvement and self-administered computer-aided exposure were all effective in reducing the flying phobia, both at post-treatment and at 1-year follow-up.[45] What is even more interesting is that there were no significant differences between these treatments in any of the outcome measures. Given the big differences in the cost and availability of these treatments, we believe that this is a good moment to determine who can benefit better from which kind of treatment. In other words, it is important to establish what the advantages are of each treatment as well as the factors that can influence the decision to choose one treatment over another.

The results of this study should be regarded with certain caution, given the relatively small number of studies and subjects involved. Similarly, the results cannot be generalized to the whole spectrum of anxiety disorders, given the limited availability of studies for

certain anxiety disorders. Even in the case of the disorders for which some randomized control trials exist, we have to note that the number of subjects and the number of studies are still rather small. For example, regarding the main comparison we report, on the primary outcome measures at post-treatment between the VRET and the evidence-based interventions, there are 15 studies and the total number of subjects is 535. All the studies have between 24 and 58 subjects, and there are five studies for the fear of flying, four studies for the panic disorder, three studies for the social phobia, two studies for arachnophobia, and only one study for acrophobia. It should be noted that in the case of fear of flying the results offer the smallest support for the conclusion we draw, and hence an increase in the number of studies and subjects per study for all the anxiety disorders would be an important step before we draw very clear conclusions.

Acknowledgments. David Opriş thanks for the financial support provided by the program cofinanced by THE SECTORAL OPERATIONAL PROGRAM FOR HUMAN RESOURCES DEVELOPMENT, Contract POSDRU 6/1.5/S/3–"DOCTORAL STUDIES, A MAJOR FACTOR IN THE DEVELOPMENT OF SOCIO-ECONOMIC AND HUMANISTIC STUDIES." Azucena García-Palacios and Cristina Botella thank for the financial support provided by PSI2010-17563 (subprograma PSIC) Ministerio de Ciencia e Innovacion, Spain.

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