Does the Exposure Method Used in Cognitive Behavioural Therapy for Panic Disorder with Agoraphobia Affect Treatment Outcome?

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Ar ekspozicijos metodika, naudojama taikant kognityvinę ir elgesio terapiją panikos sutrikimo su agorafobija gydymui, turi įtakos terapijos efektyvumui?

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SUMMARY

Panic disorder (PD) is characterized by the presence of recurrent unexpected panic attacks and persistent worrying about the occurrence of a new panic attack. 30 to 60 % of PD sufferers develop agoraphobia [PD(A)], a condition characterised by avoidance of anxiety-provoking situations, such as public transport, open or enclosed places or leaving the home alone. Cognitive Behavioral Therapy (CBT) is an effective psychological treatment for PD(A). One of its key components is exposure, a method for systematically approaching anxiety-provoking stimuli. However, up to 30% of PD(A) sufferers find traditional in vivo exposure (IVE) procedures too aversive. One way to increase the likelihood of sufferers engaging in exposure assignments is to carry them out in session. In addition, new exposure methods are being explored as alternatives to traditional IVE, such as virtual reality exposure. However, little is known about how treatment outcomes produced by these different exposure methods compare to one another.

Aim. To review relevant literature to find out whether the exposure method used affects treatment outcomes in CBT for PDA.

Method. A systematic search of the following databases was performed: CINAHL, PsychINFO, Cochrane Library, PsychArticles, Scopus, Medline, and Wed of Science. Inclusion and exclusion criteria were applied to the identified papers and the final set of studies was assessed according to methodological criteria.

Results. Eight papers were included in the review. Four papers were experimental studies comparing different modes of exposure, one paper was a retrospective naturalistic study, and three papers compared virtual reality exposure therapy (VRET)-enhanced CBT to traditional CBT. The methodological quality of the studies and the validity of their conclusions was found to be mixed.

Conclusions. The review concluded that different exposure methods tended to produce similar results. However, some indications of IVE being superior to virtual reality exposure (VRE) were found. Some findings also indicated that the combination of therapist-assisted and self-led exposure might be superior to self-led exposure only. However, studies in this area are low in numbers and of mixed quality, therfore, more high-quality research in needed.

SANTRAUKA

Įvadas. Panikos sutrikimas (PS) yra liga, kurios metu pacientai patiria stipraus nerimo (panikos) priepuolius, lydimus nuolatinio nerimavimo ir baimės, kad ištiks kitas priepuolis. Iki 60 proc. sergančiųjų patiria ir agorafobiją, t.y. baimę ir vengimą būti situacijose, provokuojančiose nerimą. Kognityvinė ir elgesio terapija (KET) yra efektyvus panikos sutrikimo su agorafobija (PSA) gydymo būdas, kurio vienas iš svarbiausių komponentų yra ekspozicija, t.y. laipsniško artėjimo prie nerimą provokuojančio stimulo metodika. Tačiau iki 30 proc. sergančiųjų PSA tradicinę ekspoziciją gyvai laiko atgrasia, todėl vienintelis būdas padidinti ekspozicijų tikimybę yra atlikti jas terapinių sesijų metu. Kita vertus, atsiranda ir kitų alternatyvų ekspozicijoms gyvai, pavyzdžiui, ekspozicija virtualioje realybėje, tačiau iki šiol mažai žinoma kokius terapinius rezultatus duoda skirtingi ekspozicijos metodai.

Tyrimo tikslas. Atlikus atitinkančią kriterijus mokslinių publikacijų apžvalgą, nustatyti ar paskelbtų mokslinių tyrimų duomenys leidžia spręsti apie skirtingų ekspozicijos metodikų efektyvumą gydant panikos sutrikimą su agorafobija.

Tyrimo metodai. Šioje literatūros apžvalgoje pateikiama sisteminio tyrimo, atlikto siekiant išsiaiškinti kokie terapijos rezultatai pasiekiami naudojant skirtingus ekspozicijos metodus, duomenys. Buvo nagrinėjamos 8 įtraukimo kriterijus atitinkančios mokslinės publikacijos. Keturios publikacijos pateikė eksperimentinius duomenis, lyginant skirtingus ekspozicijos metodus. Vienas nagrinėtas straipsnis buvo natūralistinė studija, o trys publikacijos pateikė tradicinės KET ir KET, naudojant virtualę realybę palyginimo rezultatus.

Rezultatai ir išvados. Apžvalgos rezultatai rodo, kad skirtingi ekspozicijos metodai vertinant bendrai duoda panašius terapijos rezultatus. Tačiau, buvo nustayta, kad esant specifinėms indikacijoms, ekspozicija gyvai gali būti efektyvesnė už virtualios realybės technikų taikymą, o su terapeutu daromos ekspozicijos derinimas su ekspozicija savarankiškai gali būti pranašesnis už ekspoziciją, atliekamą tik savarankiškai.

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INTRODUCTION

Definition of Panic Disorder

Panic disorder (PD) is a common psychiatric disorder primarily characterised by recurrent unexpected panic attacks [1]. Panic attack is defined as a sudden surge of strong fear or intense discomfort that is characterised by four or more of the following symptoms: palpitations; trembling or shaking; sweating; feelings of choking; sensations of shortness of breath; abdominal distress; chest pain or discomfort, feeling faint; numbness; chills or heat sensations; derealisation or depersonalisation; fear of losing control or "going crazy"; and fear of dying [1]. To meet the diagnostic criteria for PD, at least one of the attacks needs to be followed by a period of no less than one month of persistent worrying about the occurrence of a new panic attack and its consequences; and/or changes in individual's behaviour aimed at avoiding future panic attacks [1].

In the American tradition, panic attacks have been considered to be the primary pathological phenomenon and the core of the disorder, agoraphobia being an avoidance behavior secondary to it with DSM-IV considering agoraphobia a residual diagnosis [2]. From the European perspective, however, agoraphobia had always been seen as something that can occur with or without panic attacks [3]. Similarly, in DSM-V [1], panic disorder and agoraphobia are defined as two separate diagnoses.

Prevalence of Panic Disorder

European studies found that the 12-month prevalence of PD is 1.8% [2, 4]. In the United States, the lifetime prevalence of PD with or without agoraphobia is estimated to be approximately 4.7% [5].

PD rates are reported to be consistently higher among females than males [2]. The National Comorbidity Survey conducted in the USA between 1990 and 1992 showed that women were 2.5 more likely to suffer from PD than men [6]. A very recent study [7] (also found that women tended to report more severe subjective suffering than men despite similar severity symptoms as measured by an observer-rated scale.

Age of onset and typical course

The mean age of onset of PD is reported to be in the 20s [8], but both panic attacks and PD can also begin in childhood or early adolescence [3, 9]. The majority of all PD cases tend to report an onset before the age of 25 [2].

If untreated, panic disorder is usually chronic and recurrent. Wittchen et al. [10] reported that remission without treatment had been observed in 14% of cases during seven years.

Comorbidity

"Pure" PD appears to be rare; usually, it is highly comorbid with a range of other mental disorders and this pattern is consistent across available European community studies [2]. Significant associations have been found between PD and almost all anxiety, mood, substance misuse and somatoform disorders [2]. Most frequently, PD is comorbid with depressive disorders, followed by other anxiety disorders [2]. PD has also been found to be strongly associated with substance use disorders as well as somatoform disorders [11–13]. Comorbid agoraphobia is often associated with poorer treatment outcomes [14–16].

Incidence of PD co-morbid with agoraphobia has been reported to be between 35% and 65% [17]. To be diagnosed with agoraphobia, an individual must experience marked fear of and avoid two or more of the following situations: using public transportation, being in open or enclosed places, being outside of the home alone or being in a crowd or standing in line. Usually, the fear is persistent and lasts for six months or longer [1].

The 12-month prevalence of agoraphobia without PD in EU countries has been reported to be 1.3%, and the gender differences seem to be even larger than in PD, i.e. 3:1 [2]. The typical onset of Agoraphobia has also been reported to occur in the 20s, but slightly later than PD [2].

Existing treatments for Panic Disorder

Studies indicate that PD sufferers usually obtain mental health care from GPs [5]. However, half of the patients who see their GPs, are estimated not to receive anxiety- specific treatment [18]. According to some estimates, only 10% of European individuals suffering from panic disorder receive adequate treatments, i.e. pharmacological or CBT [2].

NICE guidelines in the UK [19] specify that individuals suffering from PD should be offered either a psychological treatment in the form of CBT, a pharmacological treatment by antidepressant medication or guided self-help.

An extensive meta-analysis [20] found that CBT is at least as effective as pharmacological treatments. Moreover, she also found that data on the efficacy of medication in the treatment of PD might be exaggerated by a publication bias, as studies that found non-significant results remained unpublished.

Although various treatments by antidepressant medication have been found to be effective, relapse rates following termination of these treatments are relatively high. A 15-year follow-up study of people originally treated for PD with alprazolam and imipramine, found that only 18% of the patients remained symptom free, while 51% of the patients still had anxiety attacks and received pharmacologic treatment, but appeared to have learned to cope with their anxiety symptoms and their daily functioning had improved [16]. Similar long-term outcomes have been reported in a 7-year follow-up study [21] which showed that most patients were doing well, despite the fact that some of their anxiety symptoms persisted.

A Swedish study [16] described changes in pharmacological treatment for PD in Sweden in the period between the late 1980s and 2003, as reflected in their study sample. At the end of the 1980s, 85% of the PD patients they studied continuously used benzodiazepines, in contrast to only 18% at 15-year follow-up in 2002; the opposite trend was observed in the use of antidepressants. However, Carpiniello et al. [22] reported that in the Italian PD patient cohort they had studied, 37% of patients taking drugs regularly at follow-up were on benzodiazepines, 20% were on antidepressants alone, while 43% were taking both benzodiazepines and antidepressants on a regular basis. In the UK, regular use of benzodiazepines is not recommended [19] due to their potentially damaging long-term effects, and the only recommended pharmacological interventions are either selective serotonin reuptake inhibitors (SSRIs) or tricyclic antidepressants (TCAs).

Better long-term outcomes are believed to be one of the strengths of psychological therapies for PD. For example, Clark et al. [23] demonstrated that PD patients with no, mild or

moderate agoraphobia treated with CBT were significantly less likely to endorse catastrophic interpretation of bodily sensations than individuals treated by applied relaxation or imipramine; the study also demonstrated that the stronger individuals endorsed such beliefs, the more likely they were to relapse.

Gould et al. [24] concluded in their meta-analysis that cognitive-behavioural treatments consisting of cognitive restructuring and interoceptive exposure showed the strongest effect and that CBT produced on average better results than pharmacological or combination treatments. Furthermore, they found that the gains were very well maintained at follow-up on average one year later, while pharmacological treatment showed marked slippage of gains.

A recent meta-analysis of 124 studies [20] found that both CBT and BT were effective in alleviating anxiety symptoms when treating individuals with PD with agoraphobia. However, adding the cognitive element was found to be more effective for the associated depressive symptoms and CBT also had a smaller drop-out rate compared to BT (12.7% and 18.3% respectively). CBT was found to be at least as effective as pharmacological treatment, and no difference was found between CBT only and combination treatments, consisting of CBT and a pharmacological intervention [20].

CBT treatments for panic disorder

Currently, exposure based procedures and cognitive restructuring are considered to be the core elements in the treatment of PD; exposure-based techniques usually contain both interoceptive elements for treating panic and in vivo elements for agoraphobic symptoms [20]. Exposure therapy is defined as repeated approach toward fear-provoking stimuli and has been the dominant method used in CBT for anxiety disorders since the development of these treatments [25].

Sharp, Power, and Swanson [26] demonstrated that both individual and group CBT were equally effective for PD. CBT mainly targets the perpetuating factors of panic disorder and agoraphobia, which include avoidant behaviours and cognitive biases [27].

Butler et al. [28] concluded in their review of meta-analyses that outcomes for the effectiveness of CT for PD are robust. However, psychological treatments tend to achieve better results the shorter the time since the onset of the disorder [29]. CBT has been demonstrated to be efficacious for PD without agoraphobia and for PD with agoraphobia when agoraphobia is mild to moderate [30]. However, between 26% and 40% of PD patients do not benefit significantly from CBT [30-31]. Ramnerö & Öst [32] reported that PD patients with moderate to severe agoraphobia had poorer treatment outcomes in an in vivo exposure-based therapy programme; the magnitude of change at post-treatment and follow-up was also negatively predicted by agoraphobic severity.

Cognitive Model of Panic

Clark's [33] cognitive model of panic is derived from Beck's cognitive model of depression and suggests that panic attacks are the result of catastrophic misinterpretation of certain bodily sensations and that treatment should, therefore, focus on correction of these interpretations. Clark's [33] conceptualisation of panic acknowledges that biological factors may also play a role in panic attacks, especially by increasing individual's vulnerability to such attacks although, in this model, catastrophic interpretation of bodily sensations is considered to be a necessary condition for the production of a panic attack. Further studies have demonstrated that panic attacks are consistently associated with anticipated physical, mental, or behavioural catastrophes, e.g. death, heart attack, loss of control or going crazy [34].

Behaviour-oriented Approaches

In the United States a mainly exposure-based psychological treatment for PD was developed by Barlow et al. [35]. Although the two treatment packages contain both cognitive and behavioural components, Clark's model focuses primarily on the cognitive, while Barlow's model relies to a larger extent on the behavioural techniques [36]. Nearly three decades later these two approaches are considered to be the gold standard of CBT treatments for PD and have received strongest empirical support [29] and both emphasize the concept of learned fear of bodily sensations, particularly the ones associated with autonomic arousal [25].

Sánchez-Meca et al. [29] in their meta-analysis of psychological treatments for PD proposed a predictive model for differential efficacy of the specific techniques in CBT and found that exposure seems to be the critical component in CBT for panic disorder. The authors also reported that in vivo exposure seems to be significantly more effective than exposure in imagination.

Theoretical aspects of exposure-based Treatments

Modern exposure-based treatments for anxiety disorders derive from Wolpe's [37] systematic desensitization approach [38]. However, although these treatments have been actively used for a number of decades, the theoretical understanding of why and how exposure works was slower to develop; and as a good proportion, but not all patients benefit from these treatments, a better understanding of the mechanism governing exposure-based techniques can provide new insights into why some individuals fail to benefit from them [38].

One of the most influential theories aiming to explain the mechanisms behind exposure-based interventions is Foa and Kozak's [39] emotional processing theory. Foa and Kozak [39] suggested that in exposure-based treatments certain indicators can be used to measure whether appropriate processing of fear-related information is taking place, and these are emotional arousal during exposure trials, within-session habituation (WSH; defined as decrease in physiological reactivity and reported anxiety during repeated presentations of feared stimuli) and between-session habituation (BSH; defined as decrease in the initial fearful reactions to stimuli).

Based on this theory, it was believed that levels of fear throughout exposure therapy reflect the levels of learning and are therefore very important for the therapeutic outcome; however, further research has produced mixed results in this area [40]. Furthermore, although physiological arousal usually declines within an exposure period, Craske et al. [40] conclude there is not enough data to support the idea that such declines indicate learning or can predict long-term improvement. Similarly, the authors postulate that evidence for the importance of BSH is limited as well and that the amount by which fear declines within session does not predict overall improvement.

Craske et al. [40, 25] (propose an alternative model based on the Pavlovian conditioning. In this model, it is hypothesised

that therapeutic changes in exposure-based treatments happen through extinction and that inhibitory learning is central for the extinction to take place. Inhibitory learning is based on the notion that the original association between a conditional and unconditional stimulus (CS and US) is left intact while a new learning about the relationship between the US and CS takes place [41]. This also explains how fear can again be reactivated in a different context or just by the passage of time [40].

Craske et al. [40] argue that the data on WSH and BSH mirror the effects observed by Bjork & Bjork [42] when performance during instruction has been found unable to predict the actual level of learning. Tolerance of fear is currently believed to be more critical for the success of exposure therapy than the decrease in levels of fear [25, 40].

Craske et al. [25] hypothesize that deficits in inhibitory learning may not only contribute to poor response to treatment but also contribute to the development of the pathological fear or anxiety in the first place and so methods that can enhance inhibitory learning during exposure-based treatments can be very valuable [25]. Craske et al. [25] suggest that inhibitory learning may be enhanced by expectancy violation, deepened extinction [43-44], removal of safety signals as well as providing exposure in multiple contexts. The latter has been found to decrease the likelihood of fear renewal both in laboratory studies [45] and in a clinical study [46].

Affect labeling has also been shown to solidify inhibitory learning [25]. Linguistic processing has been shown to reduce activity in the amygdala and attenuate anxiety [47]. Craske et al. [25] report routinely asking their patients to describe their emotional states while engaging in exposure.

Deacon et al. [48] found that interoceptive exposure was more effective if it continued until the individuals believed that the aversive consequences were 5% or less likely to happen. An important component of exposure is also memory consolidation after the exposure trial, which is encouraged by asking the individual to judge what they learned from the non-occurrence of the feared event, this way, the inhibitory association is strengthened [49].

The modes of exposure

Goldstein and Chambles [50] conceptualised bodily sensations as conditioned anxiety-provoking stimuli in PD patients and postulated the need to confront these stimuli using interoceptive exposure (IE). Barlow and Craske [51] define IE as deliberate induction of bodily sensations through various exercises, including head shaking, spinning, running in place or breathing through a straw with the aim to new learning experiences that may lead to a reduction of anxiety. The efficacy of IE in the treatment of PD is well demonstrated [52].

The effectiveness of in vivo exposure (IVE), or situational exposure, for PD with agoraphobia, has also been well demonstrated [53, 20, 29]. However, about 30 % of the patients fail to benefit from IVE because they find the procedure too challenging and drop out of treatment prematurely [54].

Virtual reality exposure (VRE) has been found to be effective in specific phobias [55–56]. Its advantages are that unpredictable events can be prevented, and that specific features can be created to address specific fears of the patient [57]. It has been suggested that VRE could be seen as a new way of applying both IE and IVE and may be useful in cases when patients are too afraid to confront real situations [58].

THE AIM OF THIS REVIEW

Despite the fact that the efficacy of exposure-based interventions for PD is well established, the data on whether certain modes of exposure delivery lead to better outcomes are scarce and mixed [59]. For example, Williams & Falbo [60] reported mixed results on whether the presence of the therapist improves the outcomes of IVE. Schumacher et al. [61] reported that not only patients but also therapists experience elevated levels of stress during IVE.

On the other hand, both IE and IVE are clinically feasible techniques that most mental health practitioners can implement in their practice. Therefore, more consistent data on what is most likely to help this particular client group could be beneficial. This systematic review will attempt to answer the question whether application of certain modes of exposure is more likely to produce positive treatment outcomes in PD(A) patients.

METHOD

Initial search strategy

A search of electronic databases: CINAHL, Cochrane Library, PsycInfo, PsychArticles, Scopus, Medline and Web of Science was made using the search terms below:

1. “Panic“ and “Exposure”
2. “Panic disorder” and “Exposure”
3. “Exposure” or “Exposure-based” and “panic disorder” or “panic” not “social phobia” or “social anxiety disorder” not “PTSD”
4. “Panic disorder” and “agoraphobia” not “social phobia” not “PTSD” not “trauma”

The search period was limited to 1980–2016. 1980 was chosen as the start year because that year the diagnosis of PD was introduced in DSM-III [62].

The initial searches in the listed databases produced 1790 papers. Titles revealed that many of the papers were not relevant and were removed, reducing the number to 457. The abstracts of these were examined to determine their relevance. Based on the information provided in the abstracts 428 papers were removed, and 29 papers were retained for full-text examination.

Additional searches

Initial searches produced several meta-analyses and reviews on virtual reality exposure for anxiety disorders [63–65, 56, 66–67)]. References in these meta-analyses and reviews and the selected full-text papers were examined. Six published experts in the area were contacted by e-mail. These searches produced additional three papers. Full-text versions of these papers were obtained.

Inclusion and exclusion criteria

The obtained 32 full-text articles were evaluated based on the criteria described below. As the number of articles was limited, full texts papers were examined to ensure the relevance of the selected studies. The inclusion criteria were kept quite wide as studies examining different modes of exposure delivery are rather scarce. The inclusion criteria applied for papers in this systematic review were as follows:

- Written in English, German or Spanish
- Participants meet criteria for both PD and agoraphobia
- At least two different modes of exposure delivery are compared in the study

To reduce the bias that might occur if only studies written

in the English language are included, this systematic review also aimed to include studies published in English and Spanish.

Excluded papers

Twenty-four papers were excluded from this review after full-text examination. Reasons for exclusion are detailed in Figure 1.

RESULTS

This section summarizes the findings of the reviewed papers and the analyses of their methodological strengths and weaknesses.

The process of excluding the papers at each stage is presented in Fgure 1.

Eight papers met the inclusion criteria. Two compared the effectiveness of therapist-led and self-directed IVE [59, 68]. One compared self-directed IVE and self-directed IE [69]. Two compared VRE and EIV [57–58]. Three papers compared VRE-enhanced CBT to standard CBT [70–72].

Methodological Evaluation and main findings

The main methodological characteristics are presented in Table 1.

DISCUSSION

The aim of this systematic review is to evaluate currently available research data on the influence of exposure method used in CBT for PDA on treatment outcomes. This section will discuss the findings of this review. Theoretical and clinical implications of the findings will be discussed as well, followed by the limitations of this review and suggestions for future research.

Summary of findings

The papers included in this review compared two or more exposure methods in CBT treatments for PDA. Studies 1–3 and 5 experimentally compared two or three exposure methods, while study 4 compared the implementation of exposure methods retrospectively. Papers 6–8 compared

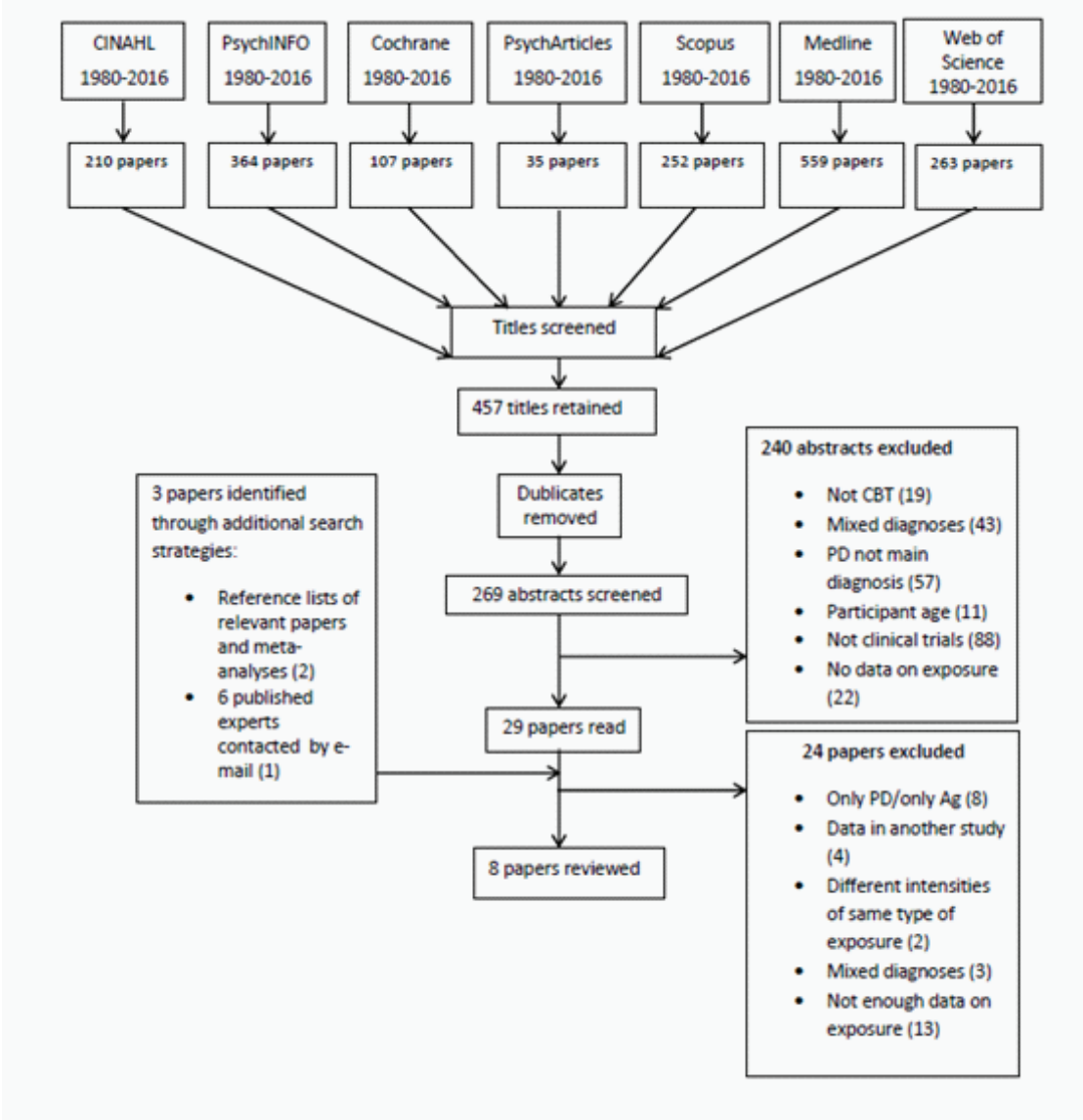

Figure 1. Flow chart showing the number of papers generated by each database search and the filtering process used to produce the final eight papers for review

Table 1. Main methodological characteristics of the reviewed studies

Study No.	Author/Year/Title/Country	Aim	Design	Attrition rate	Outcome Measures & Statistical Analyses	Results	Follow-up results	Methodological weaknesses
1	Meyerbroeker K., Morina N. ,Kerkhof G.A., Emmelkamp P.M.G. 2013 Virtual Reality Exposure Does Not Provide Any Additional Value in Agoraphobic Patients: A Randomised Controlled Trial The Netherlands	To compare virtual reality exposure therapy (VRET) and exposure in vivo in terms of outcome and processes involved.	N=55 patients diagnosed with PD and severe Agoraphobia Two active conditions: 4 sessions of CBT+ either 6 sessions of VRET or 6 sessions of exposure in vivo Wait list control	32.6 % Almost equal dropout rate from both conditions	PDSS MI-alone BSQ ACQ Analysis by repeated measures ANOVA	ITT analysis: CBT+VRET and CBT+EIV superior to no treatment on: MI-alone F(1,44)=20.185, p=0.000 BSQ F(1,44)=13.468, p=0.001 ACQ F(1,44)=30.487, p=0.000 EIV had a stronger effect on panic disorder severity as measured by PDSS (F(2,40)=8.293, p=0.001) No significant difference between the active conditions on other measures	N/A	No follow-up data Relatively small sample size Substantial number of dropouts No data on self-exposure as homework
2	Botella C., Garcia-Palacios A., Villa H., Baños R.M., Quero S., Alcañiz M., Riva G. 2007 Virtual Reality Exposure in the Treatment of Panic Disorder and Agoraphobia: A Controlled Study Spain	To study the efficacy of virtual reality exposure in the treatment of panic disorder with or without agoraphobia	N=37 patients All diagnosed with panic disorder, 82.7% of the sample also diagnosed with agoraphobia Three experimental conditions: VRE, IVE and WL control. The active treatment composed of three modules: 1) education about anxiety and PDA, cognitive restructuring and breathing training (2 sessions) 2) Exposure (IVE or VRE; 6 sessions) 3) Relapse prevention (1 session)	No data	PA record PDSS ASI FQ-Ag BDI MS CGI Analysis by repeated measures ANOVA	VRE and IVE conditions did not differ in any outcome variable Patients in both active treatments improved significantly more than subjects in the WL condition on all outcome measures. Belief in catastrophic thought F(2,34)=8.29, p<0.001), PDSS F(2,34)=15.16, p<0.0001, MS global impairment F(2,33)=3.79, p<0.05 and CGI F=(2,33)=22.793, p<0.0001; FQ-agoraphobia F (2,33)=5.88, p<0.01; ASI F(2,34)=18.55, p<0.0001 100 % in IVE and 90.9% in VRE had achieved clinical improvement (free of panic or 50% reduction in panic frequency)	12-month follow-up Both treatments equally efficacious on all variables at follow-up (no significant time x condition interaction found) Further improvement on four outcome variables: belief in catastrophic thought F(1,22)=4.48, p<0.05), PDSS F(1,22)=15.94, p<0.001, MS global impairment F(1,21)=9.56, p<0.01 and CGI F=(1,22)=6.14, p<0.05. Gains maintained on all other measures. At follow-up, 90% of the participants in IVE condition and 91.6% in VRE condition met criteria for clinical improvement (free of panic or 50% reduction in panic frequency)	No data on dropouts Small sample size Not all the participants met criteria for both panic disorder and agoraphobia (17.1 % had been diagnosed with PD without agoraphobia). 66.6 % of the sample were taking medication for PD(A)

Table 1. Main methodological characteristics of the reviewed studies

Study No.	Author/Year/Title/ Country	Aim	Design	Attrition rate	Outcome Measures & Statistical Analyses	Results	Follow-up results	Methodological weaknesses
3	Gloster A.T., Wittchen H.U., Einsle F., Helbig-Lang S., Hamm A.O., et al. 2011 Psychological Treatment for Panic Disorder With Agoraphobia: A Randomised Controlled Trial to Examine the Role of Therapist-Guided Exposure in Situ in CBT Follow up data in: Gloster A.T., Hauke Ch., Höfler M., Einsle F., Fydrich T., Hamm A., Sthröhle A., Wittchen H-U. 2013 Long-term stability of cognitive behavioral therapy effects for panic disorder with agoraphobia: A two-year follow-up study / Germany	To evaluate whether therapist-guided exposure in vivo is associated with more pervasive and long-lasting effects than therapist-prescribed exposure in vivo.	N=369 patients diagnosed with panic disorder and agoraphobia Multicenter randomised controlled trial with three experimental conditions: CBT T+, CBT T- and WL control CBT variants identical in content, structure and length, except for implementation of exposure in vivo The active treatment comprised: education, indvidualised behavioural analysis, rationale for exposure, interoceptive exposure, in vivo exposure In both active treatment conditions, participants were encouraged to engage in three exposure-related assignments each week, in T+ condition one assignment was led by the therapist, and two were self-led, in T- condition all assignments were self-led	19.6 % prior to post, additional 8.6% between post and 6 month follow-up No significant differences in attrition between T+ and T-	HAS CGI Number of panic attacks measured by PAS MI Statistical analysis: ITT Analysis by linear regressions (for dimensional variables) and cumulative logistic regressions (the categorical CGI variable) Effects tested for the second time adjusting for baseline variables, as a baseline difference on CGI was found between T+ and T- groups () Chi-square tests of independence and logistic regressions were used for binary outcomes (“yes”/”no”.)	Significant improvement on all outcome measures T+ improved more than T- on CGI ($z=1.76$, $p=0.039$) and MI ($t_{335}=3.12$, $p=0.001$) Reduction in agoraphobic avoidance accelerated after exposure was introduced Patients in T+ condition engaged in exposure assignments significantly more often and for longer in the last 24 hours prior to sessions 6–8 and 10–11; mean difference in frequency=0.64, $t_{240}=5.87$, $p<0.001$; mean difference in duration: 25.09 min, $t_{240}= 3.19$, $p<0.001$ A dose-response relationship for time X frequency of exposure and reduction in agoraphobic avoidance $t_{212}= 2.32$, $p<0.011$	*6 months follow-up:* Further improvement on all outcome measures, effect sizes ranging from 0.02 to 1.0 T+ improved further more than T- on Clinical Global Impression ($z=1.76$, $p=0.039$) and Mobility Inventory Greater reduction in panic attacks in T+ than T- ($t_{299}=1,69$, $p=0.047$) Significant increase in number of participants reporting no panic attacks in T+ group (19,1%), but no further improvement in T- group (0.7%), $t_{298}=3.26$, $p<0.001$ *24-month follow-up:* Effects sizes somewhat lower than at 6 month follow-up Most participants retained their status of responder/non-responder Agoraphobic avoidance lower in T+ group ($d=0.37$, $p<0.05$) The level of symptomatology as measured by effect size started to recede towards the post-treatment results. (Deterioration significant for HAM-A, MI and CGI, all p’s <0.05) T+ reported a significant worsening of symptoms between FU-6 and FU-24 on PAS and CGI (p’s <0.05. Patients in the T- condition reported worsening between FU-6 and FU-24 only on the MI ($p<0.05$). No significant difference between the proportion of patients who reported having sought additional treatment during the follow-up period: 35,9% in T+ condition and 38,6% in T- condition, $\chi^2(1)=0.16$, $p=.693$	Uneven sample sizes across the treatment groups: n=163 in T+ group, n=138 in T- group, n=68 in WL control group. Patients in T+ condition more frequently diagnosed with depression (49.5% vs. 37,0%, $\chi^2(1)=4.03$, $p=.045$, more likely to report at least one panic attack in the previous week (79.8% vs. 68.2%, $\chi^2(1)=5.3$, $p=.021$, and had higher global severity (CGI: M=5.4, SD=0.7 vs. M=5.2, SD=0.7,z=-2.61, $p=.009$

Table 1. (Continued)

Study No.	Author/Year/Title/ Country	Aim	Design	Attrition rate	Outcome Measures & Statistical Analyses	Results	Follow-up results	Methodological weaknesses
4	Klan T., Persike M., Hiller W. 2016 Effectiveness of Therapist-Guided exposure and Programmed Self-Exposure in the Outpatient Treatment of Panic Disorder with Agoraphobia / Germany	To examine the frequency and effectiveness of therapist-guided exposure and planned self-exposure in cognitive behavioural therapy for PDA in a university outpatient clinic.	Case series N=93 patients diagnosed with PDA Anxiety symptoms assessed before and after treatment	N/A	The German version of: MI ACQ BSQ Analysis by: Kruskal-Wallis H-Test Welch-corrected t-tests	IE modality did not have a significant effect on *agoraphobic avoidance* Significant difference in decrease in *agoraphobic avoidance b*etween a) combined IE and only therapist-led IE [t(60)=–2.12, $p<0.05$] b) No IE and combined IE [t(49)= –2.20, $p<0.05$] No significant effect of IE modality on *anxious cognitions* (ACQ) No significant effect of IE modality on f*ear of bodily sensations* (BSQ) IVE: significant effect of this exposure modality on *agoraphobic avoidance* after removing 4 outliers from the sample, [(χ^2 (2, N=85)=6.44, $p<0.05$] Significant difference in effects on *agoraphobic avoidance* between “No IVE” and “Combined IVE”: [t(71)=–3.06, $p<0.1$] Significant difference in effects on *agoraphobic avoidance* between “Combined IVE” and “Patient-led IVE” after removing 4 outliers from the sample: [t(71)=–2.12, $p<0.05$] No significant difference in *agoraphobic avoidance* between “No IV“ and “Patient-led IVE” Significant effect of IVE modality on change in ACQ scores: [(χ^2 (2, N=89)=6.02, $p<0.05$] Significant differences in change in ACQ scores between conditions “Combined IVE” and “No IVE” after removing the 4 outliers: [t(68)=–4.06, $p<0.01$] No significant effect of IVE modality on changes in fear of bodily sensations (BSQ)	No data	Non-experimental design

Table 1. *(Continued)*

Study No.	Author/Year/Title/ Country	Aim	Design	Attrition rate	Outcome Measures & Statistical Analyses	Results	Follow-up results	Methodological weaknesses
5	Ito L.M., De Arujo L.A., Tess V.L.C., De Barros-Neto T.P., Asbahr F.R., Marks I. 2001 Self-exposure therapy for panic disorder with agoraphobia / Brasil	To compare the effects of a) in vivo, b) interoceptive and c) combined in vivo and interoceptive exposure in the treatment of panic disorder and agoraphobia	N=80 outpatients randomised to one of the three forms of self-exposure (in vivo, IVE; interoceptive, IE; or combined, IVE+IE) or to a W/L control group Each treatment comprised seven sessions delivered over 10 weeks. All participants in active treatment groups received education about panic/agoraphobia and exposure, and two 45-minute sessions of therapist-assisted exposure. Participants were asked to carry out 60 minutes of daily exposure homework. At the end of treatment all participants were asked to continue doing corresponding homework assignments during follow-up and to keep a diary of this to week 62 (1-year follow-up). Both interoceptive exposure groups were trained in slow deep breathing	12%	Two phobic targets, for avoidance and fear (each score range 0–16) Four social adjustment targets (each score range 0–8) FQ ACQ Diary of panic frequency over 2 weeks BDI HAS CGI Analysis by: MANOVA (ITT) to compare the four treatment groups on main outcome measures χ^2 tests for non-parametric data and ANOVA for parametric data to compare clinical and demographic features at baseline	The three self-exposure treatments reduced panic and agoraphobia equally well. All of them improved significantly ($p<0.001$) on all 10 measures, and the improvement was significantly larger than in the control group ($p<0.001$) . The differences between the active conditions were non-significant on all measures. On phobic target avoidance the effect sizes were: d=2.5 for IVE group, d=3 for IE group and d=1.6 for IVE+IE group Patients who dropped out between week 0 and 10 were considered non-successes. Completers who improved by at least 30% on CGI scale at week 10 were rated as success. The three treatment conditions did not differ significantly on χ^2 tests regarding drop-out and success/non-success rates to week 10 or 62. Results The three groups did not differ significantly at post-treatment on responder rate. (The response criterion was a 50% or more decrease in the FQ agoraphobia sub-score between baseline and post-treatment.) Responder rates were: 45.8% in the CBT group, 42.1% in the VRET group and 35% in the WL condition. No significant differences between the active conditions on any measure.	Participants in all the active conditions kept their gains and improved further. The three self-exposure groups did not differ significantly from one another on the main outcome measures. For groups IVE, IE and IVE+IE, effects sizes increased on phobic target avoidance, CGI and HAS.	Most patients (69%) self-referred after reading an article in the lay press. 8 participants received booster sessions but this was not considered in the follow-up statistical analysis.

Table 1. (Continued)

Study No.	Author/Year/Title/ Country	Aim	Design	Attrition rate	Outcome Measures & Statistical Analyses	Results	Follow-up results	Methodological weaknesses
6	Pelissolo A., Zaoui M., Aguayo G., Nan Yao S., Roche S. et al. 2012 Virtual Reality Exposure Therapy Versus Cognitive Behavior Therapy for Panic Disorder with Agoraphobia: A Randomised Comparison Study /France and Luxembourg	To compare the effects of VRET, CBT and a WL control condition in patients with panic disorder with agoraphobia	N=92 outpatients diagnosed with PDA. Patients randomised into three groups: VRET, CBT or WL control group. Both active treatments comprised 12 one-hour sessions In the VRET group, patients received purely VRE sessions based on individually designed exposure hierarchies and using 12 available virtual environments. They were also encouraged to practice exposure in real life situations but were not given formal structured exposure homework. In CBT group, the following methods were used: individualised functional analysis, relaxation training (advised to practice relaxation for 10 min daily), provoked hyperventilation and cognitive restructuring (symptom reattribution), eliciting catastrophic automatic thoughts, prolonged exposure in imagination, graded exposure in vivo tasks, structured exposure homework.	27.2 % The rates were equal in VRET and CBT groups, 22.7% and 23.2% respectively	FQ PDSS ACQ PPGAS STAI HAS BDI GAF SDS DES WSA ERS Analysis by: Fisher's exact test; Two-level hierarchic models: logistic regression with random intercepts; Kruskall-Wallis test	The three groups did not differ significantly at post-treatment on responder rate. (The response criterion was a 50% or more decrease in the FQ agoraphobia sub-score between baseline and post-treatment.) Responder rates were: 45.8% in the CBT group, 42.1% in the VRET group and 35% in the WL condition. No significant differences between the active conditions on any measure.	*6-month:* CBT group had significantly lower scores on Disturbance subscale of FQ and Phobia 1 subscale of PPGAS. No other significant differences were found between the groups. The responder rates increased to 44% in VRET group and 56.7% in CBT group. *12-month:* No significant differences between the two active groups on any measures. Responder rates increased further to 47.6% in the VRET group and 60.7% in the CBT group.	No outcome data on control group at post No attempts to control or measure levels of self-directed exposure in the VRET group
7	Vincelli F., Anolli L., Bouchard S., Wiederhold B. K., Bcia M. B. A., Zurloni V., Riva G. 2003 Experiential Cognitive Therapy in the Treatment of Panic Disorder with Agoraphobia: A Controlled Study /Italy	To compare the effectiveness of Experiential Cognitive Therapy (ECT, comprising elements of classical CBT and VR exposure) to standard CBT and WL control	N=12 female patients diagnosed with panic disorder and agoraphobia The patients were randomly assigned to one of three conditions: ECT, CBT or WL control. In the ECT group patients received 8 therapy sessions comprising education, monitoring of panic attacks, in vivo and interoceptive exposure, VRE, cognitive restructuring, relapse prevention, three booster sessions at 1, 3, and 6 months after treatment In the CBT group patients received 12 sessions in accordance with the protocol described by Rapee & Barlow (1991) comprising cognitive restructuring, interoceptive exposure and imaginary exposure.	0	BDI-II STAI ACQ FQ Analysis by: Wilcoxon-Mann-Whitney Test Wilcoxon Signed Ranks Test Kruskal-Wallis test	Both ECT and CBT groups improved significantly on all measures (All p values <0.05 on Wilcoxon Signed Rank Test comparing pre and post values of the outcome measures.)	Unavailable	U, χ^2 and W values and effect sizes not reported No data on ACQ scores provided Small sample size No follow-up data Criteria for clinically significant improvement poorly defined. Unclear for how long the patients had been panic free when measured at post-treatment

Table 1. (Continued)

Study No.	Author/Year/Title/ Country	Aim	Design	Attrition rate	Outcome Measures & Statistical Analyses	Results	Follow-up results	Methodological weaknesses
8	Choi. Y-H.,Vincelli F., Riva G., Wiederhold B. K., Lee J-H., Park K-H. 2005 Effects of Group Experimental Cognitive Therapy for the Treatment of Panic Disorder with Agoraphobia / South Korea	To compare the effectiveness of brief ExCT (4 sessions) containing VRE component to 12 –session panic control programme (PCP; Barlow & Craske, 1994) for the treatment of PDA	N=40 patients diagnosed with PDA. The patients were randomly assigned to one of two conditions: 4 sessions of ExCT or 12 sessions of PCP	No data provided	BDI STAI ASI PBQ ACQ BSQ Analysis by t-tests	Both groups improved statistically significantly on all measures PCP group improved significantly more on PBQ at post: [t(40)=–2.17, p<0.05] Improvement on other measures did not differ significantly between conditions	6-month follow-up A significant difference (χ^2=8.47, p<0.05) in numbers of participants who had stopped medication (benzodiazepines) at follow-up (12 participants in PCP group and 4 participants in ExCT group).	No WL control group naddressed differences in numbers of participants free from medication diazepines) at baseline (40 % in ExCT group and 15% in the PCP group).

Key for abbreviations for measures used:

ACQ	Anxious Cognitions Questionnaire [73]
ASI	Anxiety Sensitivity Index [74]
BDI	Beck Depression Inventory [75]
BSQ	Body Sensations Questionnaire [73]
CGI	Clinical Global Impression [76]
DES	Dissociative Experience Scale [77]
ERS	Expectancies Rating Scale [78]
FQ	Fear Questionnaire [79]
FQ-Ag	Fear Questionnaire, Agoraphobia Subscale [79]
GAF	Global Assessment of Functioning [80]
HAS	Hamilton Anxiety Rating Scale [81]
MS	Maladjustment Scale [82]
MI	Mobility Inventory [83]
PAS	Panic and Agoraphobia Scale [84]
PBQ	Panic Belief Questionnaire [85]
PDSS	Panic Disorder Severity Scale [86]
PPGAS	Panic, Phobia and Generalised Anxiety Scale [87]
SDS	Sheehan Disability Scale [88]
STAI	State and Trait Anxiety Questionnaire [89]
WSA	Work and Social Adjustment Scale [90]

VRET-enhanced CBT to standard CBT for PDA.

In general, the reviewed papers found relatively few significant differences between the results produced by different exposure methods. A more detailed summary of the findings is provided below.

Studies 1 and 2 experimentally compared two CBT treatment protocols, one comprising VRE and another one comprising traditional IVE. In both studies these were also compared to a WL control group. Study 1 found that both active treatments produced equal results at post-treatment on all PDA-specific measures (MI-alone, ACQ and BCQ), except PDSS, on which the in IVE group did significantly better, $F(2,40)=8.293$, $p<0.001$.

Study 2 found no significant differences between the two active conditions on any outcome measures at post-treatment or 12-month follow-up. Between post-treatment and follow-up, participants in both active groups improved further on ACQ, $F(1,22)=4.48$, $p<0.05$; PDSS, $F(1,22)=15.94$, $p<0.001$; MS global impairment, $F(1,21)=9.56$, $p<0.01$; and CGI $F(1,22)=6.14$, $p<0.05$. Participants in both active groups maintained gains on all the other measures.

Study 3 compared two CBT treatment protocols, one combining in vivo therapist-led and self-led exposure and another one employing in vivo self-led exposure only. This study found that at post-treatment patients in both active conditions had improved significantly more than WL control group on all measures, but patients in the T+ condition improved more on MI ($t_{335}=3.12$, $p=0.01$) and CGI ($z=1.76$, $p=0.039$). At post-treatment, there were significantly more people in the T- group reporting no panic attacks in the previous week, than in the T+ group (47.2% vs. 58.0%), $\chi^2(1)=3.45$, $p=0.032$, but the difference was not significant when controlling for baseline values. Furthermore, at 6-month follow-up, T+ group had continued to improve significantly (19.1% increase in participants with no panic attacks in the past week), while the T- group had not (0.7%), $t_{298}=3.26$, $p<0.001$. At 24-month follow-up, the T+ groups did significantly better than T- group

on agoraphobic avoidance (MI: difference in d=0.37), p<0.05). The percentage of patients who had achieved clinically significant change in panic and agoraphobia symptoms as measured by the PAS did not differ between the T+ and T- groups at FU-24. Neither T+ nor T- achieved further improvements on any measures between FU-6 and FU-24. Although both groups were able to maintain gains, the T+ group reported a significant worsening of symptoms on PAS (d=–0.34, p=0.019) and CGI (d=–0.66, p=0.006), whereas patients in T- condition reported worsening on MI (d=–0.21, p=0.03).

Study 4 found that patients who engaged in both therapist-led and self-directed IVE, achieved greater reduction in agoraphobic avoidance as measured by MI, than those who did not engage in IVE at all, t(71)=–3.06, p<0.01, or who engaged in self-led IVE only, t(71)=–2.11, p<0.05. Combined IVE was also associated with greater improvement on ACQ than no IVE, t(68)=–4.06, p<0.01. However, no differences in improvement on BSQ were identified. Combined therapist-led and patient-led IE was found to be associated with greater reduction of MI scores than no IE, t(49)=–2.20, p<0.05. Combined IE was also more effective than only therapist-led IE in reducing MI scores: t(60)=–2.12, p<0.05

Study 5 compared three different types of self-led exposure: interoceptive, in vivo, and combined. This study found that participants in all three groups did equally well on all outcome measures (ACQ, CGI, HAS, FQ, FQAg, BDI). There were no significant differences between the active treatment groups at post-treatment, or at 6-month and 12-month follow-up. Between post-treatment and 12-month follow-up patients in all three active treatment groups continued to improve on CGI and HAS.

Studies 6, 7 and 8 looked at how VR exposure-based therapy compares to standard CBT. Study 6 found that both interventions produced equal results. However, this study failed to find statistically significant difference between the outcomes produced by the active treatment conditions and the WL control group at post-treatment, and 6-month and 12-month follow-up. At post-treatment, 45.8% of the sample in the CBT group, 42.1% in the VRET group and 35% in the WL control group met criteria for significant improvement (50% or larger reduction on the FQ-Ag). This study found that CBT group had improved significantly more than VRET group at 6-month follow-up on Disturbance Subscale of FQ and Phobia 1 Subscale of PPGAS.

Study 7 found that 12 sessions of CBT and 8 sessions of VRET produced equal results on FQ. Furthermore, participants in both groups reported no panic attacks at post-treatment.

Study 8 compared standard 12-week CBT programme for PDA to 4 sessions of experiential cognitive therapy (ExCT) comprising standard CBT techniques and VR exposure. This study found that at post-treatment participants in both active conditions were doing equally well. However, at 6-month follow-up significantly more participants in the CBT group than in the ExCT group were no longer taking anxiolytic medication to manage their PDA (χ^2=8.47, p<0.05).

In summary, although in most cases different exposure methods produced similar results in the reviewed studies, some significant differences were uncovered. On several occasions, VRET was outperformed by more classical exposure methods. In study 1, IVE produced better outcomes than VRET on PDSS; in study 6, CBT comprising IE, exposure in imagination and structured self-exposure homework outperformed VRET on FQ and PPGAS at follow-up; in study 8, PCP comprising IVE did better than VRET-enhanced ExCT on PBQ at post and on number of participants who discontinued anxiolytic medication at 6-month follow-up.

In addition, combination of therapist-led and self-led IVE was found to be superior to self-led exposure in studies 3 and 4. Participants in the therapist-assisted group in study 3 achieved better results on MI and CGI at post-treatment, and on HAS at 6-months follow-up. Similarly, study 4 found that combined (therapist-led and self-led) IE was superior to therapist-led IE only, while combined IVE was superior to self-led IVE only.

Implications for clinical practice and theory development

The reviewed studies generally report positive outcomes and large effect sizes, supporting the notion that CBT treatments comprising exposure techniques are efficacious in treatment of PDA. However, several authors have pointed out that exposure is not routinely used in clinical practice despite of the solid evidence supporting the safety and effectiveness of these methods [91-93]. This is also mirrored in the reviewed studies, with experimental studies having allocated a considerably larger proportion of the therapy time to exposure assignments than the retrospective naturalistic study.

IVE has accumulated a strong evidence base as key treatment ingredient for PDA, including positive outcomes at long-term follow-up (up to 14 years) [94, 95]. The efficacy of IVE, which sometimes exceeded that of other modalities, was further demonstrated in the reviewed studies.

VRE has been demonstrated to produce promising outcomes in treatment of specific phobias [96-97]. The reviewed studies found that VRE can produce almost equally good results in PDA patients as IVE, both short- and longer-term. Furthermore, VRE was shown to be effective for severely impaired patients. However, the hopes that VRE could be a more acceptable alternative than IVE, which up to 30% of patients find too aversive [54], have not been confirmed in the reviewed studies. Page [98] criticised the research on VRET in anxiety disorders for small sample sizes. This was also the case in the reviewed studies. Therefore, the findings need to be to interpreted with caution and more research is indicated.

The findings in the reviewed studies indicated that therapist-assisted and self-led exposure produced almost equal outcomes, with therapist-assisted exposure being slightly superior in reducing agoraphobic avoidance. This is a promising finding in the context of low-intensity CBT, which can be delivered online or over the phone, and implies that the therapist is not able to participate in exposure assignments. At the same time, the findings suggest that whenever possible, incorporating therapist-assisted exposure in session might be beneficial, especially for reduction of agoraphobic avoidance, which has been demonstrated to predict long-term stability of treatment gains [99].

Furthermore, participants in most reviewed studies engaged in several types of exposure across the conditions, which again might have contributed to the positive outcomes through the consolidation of learning in various contexts [25].

The evidence from the reviewed studies further support the effectiveness of exposure-based techniques for PDA. The

reviewed studies were conducted in seven different countries yet produced similar results, suggesting the universality of CBT based treatments. Similar conclusions were drawn by Kenardy et al. [100] in a study investigating the effectiveness of standard CBT for PD in Scotland and Australia. This study concluded that "treatment effectiveness is robust to cultural difference" (p. 1074).

Summary of the methodological evaluation

The reviewed studies varied in their methodological quality. While studies 1 and 3 succeeded to control for most extraneous variables and compared two otherwise identical treatment packages where the only difference was the exposure method, the rest of the studies had some serious methodological problems. Study 2 did not provide any data on attrition and failed to report whether participants were encouraged to engage in exposure homework. Study 4 was a retrospective study, so it is not possible to draw any conclusions on causal effects of the interventions, as no extraneous variables had been controlled. In study 5 which studied effects of self-led exposure, all the participants received two sessions of therapist-led exposure first. This might have affected the patients' ability to engage in self-led exposure later in treatment. In study 6, participants in the VRET condition were encouraged to regularly engage in self-led in vivo exposure between sessions, making it difficult to separate between the effects of VRET and self-led IVE. Similarly, in Study 7, participants who received VRET, were encouraged to engage in graded self-exposure between sessions, and each session started with the review of the homework. In contrast, participants in the CBT condition in this study did not receive in vivo exposure in sessions and the study did not provide any data on what kind of homework participants in this condition were asked to do.

In study 8, the ExCT condition, which included VRE exposure, consisted of 4 sessions only, in contrast to the CBT condition which comprised 12 sessions. As the two conditions differed so greatly in the length of intervention, it is difficult to establish whether the relative poorer long-term outcomes in the ExCT group were the result of the specific components of the intervention, or its inadequate length. Furthermore, participants in ExCT condition underwent both IE and IVE in session, again making it difficult to distinguish between the effects of VRET and other types of exposure.

Sample sizes in the studies were also very different. Study 3 was the biggest study and had 369 participants, while study 7 had only 12. None of the studies provided a priori sample size calculations.

In addition to that, the samples in the studies varied considerably in complexity. While studies 1, 5 and 7 excluded patients with the comorbid MDD, 37.7% of the patients in study 3 and 17% of the patients in study 4 were diagnosed with comorbid depression at baseline. Roy Byrne et al. [101] found that people with comorbid lifetime major depression reported a larger number of physiological symptoms during their panic attacks and that both current and lifetime depression-panic comorbidity was associated with more severe, persistent and disabling illness.

In summary, criticisms of the reviewed studies include small sample sizes and possible lack of statistical power, scarcity of long-term follow-up data and limited control of confounding variables.

Overall the findings of this systematic review demonstrate that various exposure-based methods produce positive and similar short-term and longer-term outcomes, although IVE, especially when administered both in session and as homework, may produce superior outcomes. However, these results should be interpreted with caution, as identified methodological weaknesses in a number of the reviewed studies make it difficult to draw robust conclusions. Further high-quality research is clearly needed.

Limitations of this review

When interpreting the findings of this systematic review it is important to take its limitations into account. The quality of search has a crucial effect on the validity of the results of a systematic review [102]. Attempts were made to identify relevant papers by searching a high variety of databases and examining the reference lists of papers and meta-analyses. However, there is always a risk of papers being missed. In addition, although this review aimed to include papers published in English, German and Spanish, the search was performed only in the international databases predominantly containing English language papers. Therefore, German or Spanish papers could still have been missed. Furthermore, there may be some relevant research published in other languages that was not addressed.

The studies were identified and reviewed only by the author, leading to potential risk for subjectivity. Furthermore, all the included papers were published in peer-reviewed journals, which are more likely to publish papers reporting promising treatment effects [102].

Suggestions for future research

Future research should aim to study long-term outcomes produced by various exposure methods. More high-quality research is needed to establish the effectiveness of virtual reality exposure in the treatment of PDA. Only one reviewed study reported how much time participants spent engaging in exposure. The question of how much exposure is needed to produce satisfactory outcomes could also be addressed in future research. Furthermore, non-responders remain an important issue. One way of addressing this challenge could be to look at whether individuals who do not respond to a particular method of exposure would respond to exposure exercises delivered through a different modality.

CONCLUSION

Although CBT is the psychological treatment of choice for PDA, and exposure is an integral component of most CBT for PDA protocols, surprisingly few studies have looked little at how different modalities of exposure delivery compare to one another.

Although the currently available data suggests that different exposure modalities tend to produce similar results, there are some indications of IVE possibly producing somewhat superior outcomes to VRE and exposure delivered both in session and as homework leading to a larger reduction in agoraphobic avoidance than only self-led exposure. However, due to very small number of studies and a number of methodological issues in particular regarding non-inferiority trials, more high-quality research with larger samples is clearly needed.

LITERATŪRA

1. Diagnostic and statistical manual of mental disorders: DSM-5. Washington: American Psychiatric Publishing; 2014.
2. Goodwin R, Faravelli C, Rosi S, Cosci F, Truglia E, Graaf RD, et al. The epidemiology of panic disorder and agoraphobia in Europe. European Neuropsychopharmacology. 2005;15(4):435–43.
3. Reed V, Wittchen H-U. Dsm-iv panic attacks and panic disorder in a community sample of adolescents and young adults: how specific are panic attacks? Journal of Psychiatric Research. 1998Jan;32(6):335–45.
4. Wittchen H, Jacobi F, Rehm J, Gustavsson A, Svensson M, Jönsson B, et al. The size and burden of mental disorders and other disorders of the brain in Europe 2010. European Neuropsychopharmacology. 2011;21(9):655–79.
5. Kessler RC, Chiu WT, Jin R, Ruscio AM, Shear K, Walters EE. The Epidemiology of Panic Attacks, Panic Disorder, and Agoraphobia in the National Comorbidity Survey Replication. Archives of General Psychiatry. 2006Jan;63(4):415.
6. Kessler RC. Lifetime and 12-Month Prevalence of DSM-III-R Psychiatric Disorders in the United States. Archives of General Psychiatry. 1994Jan;51(1):8.
7. Pesce L, Veen TV, Carlier I, Noorden MSV, N. J. A. Van Der Wee, Hemert AMV, et al. Gender differences in outpatients with anxiety disorders: the Leiden Routine Outcome Monitoring Study. Epidemiology and Psychiatric Sciences. 2015;25(03):278–87.
8. Weissman MM. The Cross-national Epidemiology of Panic Disorder. Archives of General Psychiatry. 1997Jan;54(4):305.
9. Vollrath M, Koch R, Angst J. The Zurich study. European Archives of Psychiatry and Neurological Sciences. 1990;239(4):221–30.
10. Wittchen H, Essau CA, Krieg J. Anxiety disorders: Similarities and differences of comorbidity in treated and untreated groups. British Journal of Psychiatry. 1991;159 (SEPT. SUPPL. 12), 23–33.
11. Merikangas KR, Angst J, Eaton W, Canino G, Rubio-Stipec M, Wacker H, et al. Comorbidity and boundaries of affective disorders with anxiety disorders and substance misuse: Results of an international task force. The British Journal of Psychiatry. 1996; Supplement, (30), 58–67.
12. Wittchen H-U, Reed V, Kessler RC. The Relationship of Agoraphobia and Panic in a Community Sample of Adolescents and Young Adults. Archives of General Psychiatry. 1998Jan;55(11):1017.
13. Faravelli C, Abrardi L, Bartolozzi D, Cecchi C, Cosci F, D'Adamo D, et al. The Sesto Fiorentino Study: Point and One-Year Prevalences of Psychiatric Disorders in an Italian Community Sample Using Clinical Interviewers. Psychotherapy and Psychosomatics. 2004Aug;73(4):226–34.
14. Noyes R. Outcome of Panic Disorder. Archives of General Psychiatry. 1990Jan;47(9):809.
15. Katschnig H, Amering M. The Long-Term Course of Panic Disorder and Its Predictors. Journal of Clinical Psychopharmacology. 1998;18.
16. Andersch S, Hetta J. A 15-year follow-up study of patients with panic disorder. European Psychiatry. 2003;18(8):401–8.
17. Wittchen H-U, Gloster AT, Beesdo-Baum K, Fava GA, Craske MG. Agoraphobia: a review of the diagnostic classificatory position and criteria. Depression and Anxiety. 2010;27(2):113–33.
18. Kroenke K, Spitzer RL, Williams JB, Monahan PO, Löwe B. Anxiety Disorders in Primary Care: Prevalence, Impairment, Comorbidity, and Detection. Annals of Internal Medicine. 2007Jun;146(5):317.
19. NICE. Generalized anxiety disorder and panic disorder (with or without agoraphobia) in adults: Management in primary, secondary, and community care. 2011; NICE clinical guideline 113.
20. Mitte K. A meta-analysis of the efficacy of psycho- and pharmacotherapy in panic disorder with and without agoraphobia. Journal of Affective Disorders. 2005;88(1):27–45.
21. Noyes R, Clancy J, Woodman C, Holt CS, Suelzer M, Christiansen J, et al. Environmental Factors Related to the Outcome of Panic Disorder. The Journal of Nervous and Mental Disease. 1993;181(9):529–38.
22. Carpiniello B, Baita A, Carta MG, Sitzia R, Macciardi AM, Murgia S, et al. Clinical and psychosocial outcome of patients affected by panic disorder with or without agoraphobia: results from a naturalistic follow-up study. European Psychiatry. 2002;17(7):394–8.
23. Clark DM, Salkovskis PM, Ost L-G, Breitholtz E, Al E. Misinterpretation of body sensations in panic disorder. Journal of Consulting and Clinical Psychology. 1997;65(2):203–13.
24. Gould RA, Ott MW, Pollack MH. A meta-analysis of treatment outcome for panic disorder. Clinical Psychology Review. 1995;15(8):819–44.
25. Craske MG, Treanor M, Conway CC, Zbozinek T, Vervliet B. Maximizing exposure therapy: An inhibitory learning approach. Behaviour Research and Therapy. 2014;58:10–23.
26. Sharp DM, Power KG, Swanson V. A comparison of the efficacy and acceptability of group versus individual cognitive behaviour therapy in the treatment of panic disorder and agoraphobia in primary care. Clinical Psychology & Psychotherapy. 2004;11(2):73–82.
27. Arch JJ, Craske MG. Addressing Relapse in Cognitive Behavioral Therapy for Panic Disorder: Methods for Optimizing Long-Term Treatment Outcomes. Cognitive and Behavioral Practice. 2011;18(3):306–15.
28. Butler A, Chapman J, Forman E, Beck A. The empirical status of cognitive-behavioral therapy: A review of meta-analyses. Clinical Psychology Review. 2006;26(1):17–31.
29. Sánchez-Meca J, Rosa-Alcázar AI, Marín-Martínez F, Gómez-Conesa A. Psychological treatment of panic disorder with or without agoraphobia: A meta-analysis. Clinical Psychology Review. 2010;30(1):37–50.
30. Barlow DH. Anxiety and its disorders: the nature and treatment of anxiety and panic. New York: Guilford Press; 2004.
31. Marcaurelle R, Bélanger C, Marchand A, Katerelos TE, Mainguy N. Marital predictors of symptom severity in panic disorder with agoraphobia. Journal of Anxiety Disorders. 2005;19(2):211–32.
32. Ramnerö J, Öst L-G. Prediction of outcome in the behavioural treatment of panic disorder with agoraphobia. Cognitive Behaviour Therapy. 2004;33(4):176–80.
33. Clark DM. A cognitive approach to panic. Behaviour Research and Therapy. 1986;24(4):461–70.
34. Clark DM, Salkovskis PM, Ost L-G, Breitholtz E, Al E. Misinterpretation of body sensations in panic disorder. Journal of Consulting and Clinical Psychology. 1997;65(2):203–13.
35. Barlow DH, Craske MG, Cerny JA, Klosko JS. Behavioral treatment of panic disorder. Behavior Therapy. 1989;20(2):261–82.
36. Rachman S. Psychological Treatment of Anxiety: The Evolution of Behavior Therapy and Cognitive Behavior Therapy. Annual Review of Clinical Psychology. 2009;5(1):97–119.
37. Wolpe J. Psychotherapy by reciprocal inhibition. Stanford, CA: Univ. Press; 1974.
38. Mcnally RJ. Mechanisms of exposure therapy: How neuroscience can improve psychological treatments for anxiety disorders. Clinical Psychology Review. 2007;27(6):750–9.
39. Foa EB, Kozak MJ. Emotional processing of fear: Exposure to corrective information. Psychological Bulletin. 1986;99(1):20–35.
40. Craske MG, Kircanski K, Zelikowsky M, Mystkowski J, Chowdhury N, Baker A. Optimizing inhibitory learning during exposure therapy. Behaviour Research and Therapy. 2008;46(1):5–27.
41. Bouton ME. Context, time, and memory retrieval in the interference paradigms of Pavlovian learning. Psychological Bulletin. 1993;114(1):80–99.
42. Bjork RA, Bjork EL. Optimizing treatment and instruction: Implications of a new theory of disuse. Memory and society: Psychological perspectives. New York, US: Psychology Press; 2006. p. 116–40.
43. Rescorla RA. Extinction can be enhanced by a concurrent excitor. Journal of Experimental Psychology: Animal Behavior Processes. 2000;26(3):251–60.
44. Rescorla RA. Deepened extinction from compound stimulus presentation. Journal of Experimental Psychology: Animal Behavior Processes. 2006;32(2):135–44.
45. Bandarian BS, Neumann DL, Boschen MJ. Context effects on memory retrieval following the Pavlovian extinction process in humans and its application in the reduction of return of fear. In Neumann DL & Andrews G (Eds), Beyond the lab: Applications of cognitive research in memory and learning. 2011; New York: Nova Science Publishers
46. Vansteenwegen D, Vervliet B, Iberico C, Baeyens F, Vandenbergh O, Hermans D. The repeated confrontation with videotapes of spiders in multiple contexts attenuates renewal of fear in spider-anxious students. Behaviour Research and Therapy. 2007;45(6):1169–79.
47. Lieberman MD, Eisenberger NI, Crockett MJ, Tom SM, Pfeifer JH, Way BM. Putting Feelings Into Words: Affect Labeling Disrupts Amygdala Activity in Response to Affective Stimuli. Psychological Science. 2007Jan;18(5):421–8.
48. Deacon B, Kemp JJ, Dixon LJ, Sy JT, Farrell NR, Zhang AR. Maximizing the efficacy of interoceptive exposure by optimizing inhibitory learning: A randomized controlled trial. Behaviour Research and Therapy. 2013;51(9):588–96.
49. Meeter M, Murre JMJ. Consolidation of Long-Term Memory: Evidence and Alternatives. Psychological Bulletin. 2004;130(6):843–57.
50. Goldstein AJ, Chambless DL. A reanalysis of agoraphobia. Behavior Therapy. 1978;9(1):47–59.
51. Barlow DH, Craske MG, Craske MG. Mastery of your anxiety and panic: MAP-3: client workbook for anxiety and panic. New York: Oxford University Press; 2000.
52. Lee K, Noda Y, Nakano Y, Ogawa S, Kinoshita Y, Funayama T, et al. Interoceptive hypersensitivity and interoceptive exposure in patients with panic disorder: specificity and effectiveness. BMC Psychiatry. 2006;6(1).
53. Emmrich A, Beesdo-Baum K, Gloster AT, Knappe S, Höfler M, Arolt V, et al. Depression Does Not Affect the Treatment Outcome of CBT for Panic and Agoraphobia: Results from a Multicenter Randomized Trial. Psychotherapy and Psychosomatics. 2012;81(3):161–72.
54. Emmelkamp P, Krijn M, Hulsbosch A, Vries SD, Schuemie M, Mast CVD. Virtual reality treatment versus exposure in vivo: a comparative evaluation in acrophobia. Behaviour Research and Therapy. 2002;40(5):509–16.
55. Meyerbroeker K, Powers MB, Stegeren AV, Emmelkamp PM. Does Yohimbine Hydrochloride Facilitate Fear Extinction in Virtual Reality Treatment of Fear of Flying A Randomized Placebo-Controlled Trial. Psychotherapy and Psychosomatics. 2012;81(1):29–37.
56. Powers MB, Emmelkamp PM. Virtual reality exposure therapy for anxiety disorders: A meta-analysis. Journal of Anxiety Disorders. 2008;22(3):561–9.
57. Meyerbroeker K, Morina N, Kerkhof G, Emmelkamp P. Virtual Reality Exposure Therapy Does Not Provide Any Additional Value in Agoraphobic Patients: A Randomized Controlled Trial. Psychotherapy and Psychosomatics. 2013;82(3):170–6.
58. Botella C, García-Palacios A, Villa H, Baños RM, Quero S, Alcañiz M, et al. Virtual reality exposure in the treatment of panic disorder and agoraphobia: A controlled study. Clinical Psychology & Psychotherapy. 2007;14(3):164–75.
59. Gloster AT, Wittchen H-U, Einsle F, Lang T, Helbig-Lang S, Fydrich T, et al. Psychological treatment for panic disorder with agoraphobia: A randomized controlled trial to examine the role of therapist-guided exposure in situ in CBT. Journal of Consulting and Clinical Psychology. 2011;79(3):406–20.
60. Williams S, Falbo J. Cognitive and performance-based treatments for panic attacks in people with varying degrees of agoraphobic disability. Behaviour Research and Therapy. 1996;34(3):253–64.
61. Schumacher S, Gaudlitz K, Plag J, Miller R, Kirschbaum C, Fehm L, et al. Who is stressed? A pilot study of salivary cortisol and alpha-amylase concentrations in agoraphobic patients and their novice therapists undergoing in vivo exposure. Psychoneuroendocrinology. 2014;49:280–9.
62. Spitzer RL. DSM-III: diagnostic and statistical manual of mental disorders. Washington: APA; 1981.
63. Opriş D, Pintea S, García-Palacios A, Botella C, Szamosközi Ş, David D. Virtual reality exposure therapy in anxiety disorders: a quantitative meta-analysis. Depression and Anxiety. 2011Jul;29(2):85–93.
64. Page S, Coxon M. Virtual Reality Exposure Therapy for Anxiety Disorders: Small Samples and No Controls? Frontiers in Psychology. 2016Nov;7.
65. Ling Y, Nefs HT, Morina N, Heynderickx I, Brinkman W-P. A Meta-Analysis on the Relationship between Self-Reported Presence and Anxiety in Virtual Reality Exposure Therapy for Anxiety Disorders. PLoS ONE. 2014Jun;9(5).
66. Parsons TD, Rizzo AA. Affective outcomes of virtual reality exposure therapy for anxiety and specific phobias: A meta-analysis. Journal of Behavior Therapy and Experimental Psychiatry. 2008;39(3):250–61.
67. Turner WA, Casey LM. Outcomes associated with virtual reality in psychological interventions: where are we now? Clinical Psychology Review. 2014;34(8):634–44.
68. Klan T, Persike M, Hiller W. Effectiveness of therapist-guided exposure and programmed self-exposure in the outpatient treatment of panic disorder with agoraphobia. [Therapeutenbegleitete und patientengeleitete exposition bei panikstörung mit agoraphobie: Eine studie zur einsatzhäufigkeit und effektivität in der routineversorgung] Zeitschrift Fur Klinische Psychologie Und Psychotherapie. 2016; 45(1),36–48.
69. Ito LM. Self-exposure therapy for panic disorder with agoraphobia: Randomised controlled study of external v. interoceptive self-exposure. The British Journal of Psychiatry. 2001Jan;178(4):331–

6.

70. Vincelli F, Anolli L, Bouchard S, Wiederhold BK, Zurloni V, Riva G. Experiential cognitive therapy in the treatment of panic disorders with agoraphobia: A controlled study. CyberPsychology & Behavior. 2003;6(3), 321–328.

71. Choi Y, Vincelli F, Riva G, Wiederhold BK, Lee J, Park K. Effects of group experiential cognitive therapy for the treatment of panic disorder with agoraphobia. Cyberpsychology and Behavior. 2005; 8(4), 387–393.

72. Pelissolo A, Zaoui M, Aguayo G, Yao SN, Roche S, Ecochard R, et al. Virtual reality exposure therapy versus cognitive behavior therapy for panic disorder with agoraphobia: A randomized comparison study. Journal of Cybertherapy and Rehabilitation, 2012;5(1), 35–43.

73. Chambless DL, Caputo GC, Bright P, Gallagher R. Assessment of fear of fear in agoraphobics: The Body Sensations Questionnaire and the Agoraphobic Cognitions Questionnaire. Journal of Consulting and Clinical Psychology. 1984;52(6):1090–7.

74. Reiss S, Peterson RA, Gursky DM, Mcnally RJ. Anxiety sensitivity, anxiety frequency and the prediction of fearfulness. Behaviour Research and Therapy. 1986;24(1):1–8.

75. Beck, Aaron T., Robert A. Steer, and Margery G. Carbin. "Psychometric properties of the Beck Depression Inventory: Twenty-five years of evaluation." Clinical Psychology Review 8, no. 1 (1988): 77–100.

76. Guy W (Ed.). ECDEU assessment manual for psychopharmacology. Rockville, MD, U.S.: Department of Health, Education, and Welfare, 1976.

77. Bernstein E, Putnam FW. Development, reliability, and validity of a dissociation scale. Journal of Nervous and Mental Disease. 1986;174(12):727 –735.

78. Bouvard M, Cottraux J. Protocoles et échelles d'évoluation en psychiatrie et en psychologie. Paris: Masson; 2005.

79. Marks IM. Brief standard self-rating for phobic patients. Behaviour Research and Therapy. 1979;17(3): 263–267.

80. Global Assessment of Functioning. Handbook of Disease Burdens and Quality of Life Measures. 2010:4216–4220.

81. Hamilton M. The assessment of anxiety states by rating. British Journal of Medical Psychology. 1959;32(1): 50–55.

82. Echeburúa E, Corral P, Fernández-Montalvo J. Escala de inadaptación: Propiedades psicométricas en contextos cĺinicos. Análisis y Modificación De Conducta. 2000; 26: 325–340.

83. Chambless DL, Sharpless BA, Rodriguez D, McCarthy KS, Milrod BL, Khalsa, S et al. Psychometric properties of the mobility inventory for agoraphobia: Convergent, discriminant, and criterion-related validity. Behavior Therapy. 2001, 42(4): 689–699.

84. Bandelow B, Brunner E, Broocks A, Beinroth D, Hajak G, Pralle L, et al. The use of the Panic and Agoraphobia Scale in a clinical trial. Psychiatry Research. 1998;77(1):43–9.

85. Greenberg R. Panic disorder and agoraphobia. In Scott J, Williams J, Beck AT (Eds.), Cognitive therapy in clinical practice: An illustrative casebook (pp. 25–49) Routledge, 1989.

86. Shear MK, Brown TA, Sholomskas DE, Barlow DH, Gorman JM, Woods SW, et al. Panic disorder severity scale (PDSS). Pittsburg: Department of Psychiatry, University of Pittsburg School of Medicine, 1992.

87. Cottraux J, Bouvard M, Legeron P. Méthodes et échelles d'évaluation des comportements Issy les Moulineaux: Editions d'Application Psychotechniques, 1985.

88. Sheehan DV. The measurement of disability. International Clinical Psychopharmacology. 1996; 11(SUPPL. 3): 89–95.

89. Spielberger C. State-trait anxiety inventory: A comprehensive bibliography. Palo Alto, CA: Consulting Psychologists Press, 1983.

90. Mataix-Cols D, Cowley AJ, Hankins M, Schneider A, Bachofen M, Kenwright M, et al. Reliability and validity of the Work and Social Adjustment Scale in phobic disorders. Comprehensive Psychiatry. 2005;46(3):223–8.

91. Böhm K, Förstner U, Külz A, Voderholzer U. Health care provision for patients with obsessive compulsive disorder: Is exposure treatment used? [Versorgungsrealität der zwangsstörungen: Werden expositionsverfahren eingesetzt?] Verhaltenstherapie. 2008; 18(1): 18–24.

92. Roth C, Siegl J, Aufdermauer N, Reinecker H. Therapy of anxiety and obsessive-compulsive disorder in behavior therapy practice. [Therapie von angst- und zwangspatienten in der verhaltenstherapeutischen praxis] Verhaltenstherapie.2004; 14(1): 16–21.

93. Olatunji BO, Deacon BJ, Abramowitz JS. The Cruelest Cure? Ethical Issues in the Implementation of Exposure-Based Treatments. Cognitive and Behavioral Practice. 2009;16(2):172–80.

94. Peter H, Brückner E, Hand I, Rohr W, Rufer M. Treatment outcome of female agoraphobics 3–9 years after exposure in vivo: A comparison with healthy controls. Journal of Behavior Therapy and Experimental Psychiatry. 2008;39(1):3–10.

95. Fava GA, Rafanelli C, Grandi S, Conti S, Ruini C, Mangelli L, et al. Long-term outcome of panic disorder with agoraphobia treated by exposure. Psychological Medicine. 2001;31(05).

96. Emmelkamp P, Krijn M, Hulsbosch A, Vries SD, Schuemie M, Mast CVD. Virtual reality treatment versus exposure in vivo: a comparative evaluation in acrophobia. Behaviour Research and Therapy. 2002;40(5):509–16.

97. Garcia-Palacios A, Hoffman H, Carlin A, Furness T, Botella C. Virtual reality in the treatment of spider phobia: a controlled study. Behaviour Research and Therapy. 2002;40(9):983–93.

98. Page S, Coxon M. Virtual Reality Exposure Therapy for Anxiety Disorders: Small Samples and No Controls? Frontiers in Psychology. 2016Nov;7.

99. Dow MGCAT, Kenardy JA, Johnston DW, Newman MG, Taylor CB, Thomson A. Prognostic indices with brief and standard CBT for panic disorder: I. Predictors of outcome. Psychological Medicine. 2007Oct;37(10).

100. Kenardy JA, Dow MGT, Johnston DW, Newman MG, Thomson A, Taylor CB. A Comparison of Delivery Methods of Cognitive-Behavioral Therapy for Panic Disorder: An International Multicenter Trial. Journal of Consulting and Clinical Psychology. 2003;71(6):1068–75.

101. Roy-Byrne PP. Lifetime panic-depression comorbidity in the National Comorbidity Survey: Association with symptoms, impairment, course and help-seeking. The British Journal of Psychiatry. 2000Jan;176(3):229–35.

102. Hemingway P, Brereton N. What is a systematic review? 2009; Retrieved 9/25, 2016, from http://www.medicine.ox.ac.uk/bandolier/painres/download/whatis/syst-review.pdf

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