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Research report

# CBT for pharmacotherapy non-remitters—a systematic review of a next-step strategy

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ABSTRACT

*Background:* Non-remission rates to pharmacotherapy for anxiety disorders are related to higher relapse rates, decreased quality of life and greater functional impairment. Here we sought to investigate the efficacy of cognitive-behavior therapy (CBT) as a next-step strategy in the treatment of patients with anxiety disorders who did not remit after a pharmacological intervention.

*Method:* We carried out a systematic review in the ISI, Pubmed and PsycINFO/PsychLit databases. Studies that did not use CBT and that did not focus on resistance to drug therapy were excluded. We considered resistant patients who failed to respond (did not fully remit) to an adequate trial of pharmacotherapy and still exhibited residual symptoms of anxiety disorder.

*Results:* We identified 603 references in our survey, of which 17 were included: eight were on OCD, five on panic disorder, and four on PTSD. No studies were found on social anxiety disorder and generalized anxiety disorder. We observed a lack of standardization of terminology and of definitions of resistance, which makes comparison of results difficult. Finally, all of the identified studies showed benefits from the addition of CBT as a next-step strategy.

*Limitations:* A limited number of randomized controlled studies were found.

*Conclusions:* CBT seems to be a promising next-step strategy for patients with anxiety disorders who did not remit with drug-based therapies. However, further clinical trials with strong methodological designs are needed to definitely establish its efficacy in this population.



## 1. Introduction

There is consistent evidence about the efficacy of cognitive-behavior therapy (CBT) and pharmacotherapy in the treatment of anxiety disorders. CBT is considered as a first-line treatment for some anxiety disorders. In posttraumatic stress disorder (PTSD), experts' guidelines recommend CBT or drug therapy as the first choice of treatment, which are also effective for the co-morbid depression and anxiety disorders. It has been shown that the addition of CBT to the treatment of patients with resistance to drug therapy leads to better outcomes than standard pharmacological treatment alone (Foa, 2009). For obsessive–compulsive disorder (OCD), the most effective first-line treatments are the selective serotonin reuptake inhibitors (SSRIs) or CBT (particularly exposure and response prevention) (Fenske and Schwenk, 2009; Koran, 2007). In panic disorder as well, there is strong evidence of the efficacy of drug therapy and CBT as initial treatments. However, the available results are not enough to

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recommend combined treatments (drug therapy + CBT) as superior to monotherapy or an intervention as superior to another (Stein, 2009).

CBT has a number of potential gains over pharmacotherapy in the treatment of anxiety disorders: fewer adverse effects, smaller relapse rates (Etten and Taylor, 1998), greater adhesion rate (Mitte, 2005), and greater acceptability (Hofmann, 1998). Pharmacotherapy has such disadvantages as more side effects and rates of relapse with discontinued medication (Simpson, Gorfinkle and Liebowitz, 1999). Nevertheless, in practice CBT is much less used, especially because of the limited availability of specialized practitioners. Moreover, pharmacological treatments have received much more attention from the marketing than psychosocial interventions such as CBT have (Insel, 2009). These reasons account for the fact that drug therapy is now viewed by most clinicians—for bad or for good—as the first choice in the treatment of anxiety disorders.

Non-remission of anxiety disorders to pharmacotherapy or to psychotherapy has turned out to be a crucial issue. The presence of residual symptoms is known to be associated with higher relapse rates, decreased quality of life and greater functional impairment (Fava and Tomba, 2009). It is, therefore, increasingly important to think of therapeutic alternatives for patients with anxiety disorders who do not remit after pharmacological treatment. The purpose of the present article is to find and review the available evidence of the efficacy of CBT as a next-step strategy in the treatment of patients who failed to improve significantly despite drug therapy. As far as we know, this is the first systematic review on the subject.

## 2. Methods

### 2.1. Search methods

Electronic searches were performed in the ISI, PubMed and PsycINFO/PsychLit databases, including all languages and all years, until December 08, 2009. The following terms were used:

ISI (advanced search):

- TS = ("behavi* therapy" OR "cognitive therapy" OR "cognitive behavio* therapy" OR "exposure therapy" OR "exposure treatment" OR "exposure session*" OR CBT OR "cognitive reest*" OR "anxiety manage*" OR flooding OR "systematic desens*")
- TS = (anxiety OR phob* OR panic OR OCD OR obsess* OR PTSD OR "stress disorder*" OR GAD)
- TS = (resist* OR refract* OR non-respons* OR non-respond* OR nonrespond* OR augment* OR "sequential treatment" OR "addition of CBT" OR "partial respond*" OR "crossover treatment*" OR "second-line treatment*" OR "second-line recommendation*" OR "fail to respond" OR "second level option*" OR "fail* to respond*" OR "fail* to fully respond*" OR "prior medication trial" OR non-remit* OR nonremit* OR "remain* sympt*")

All of the 3 citation databases were activated [Science Citation Index Expanded (SCI-EXPANDED), Social Sciences Citation Index (SSCI) and Arts & Humanities Citation Index (A&HCI)], and we restricted the search criteria in order to include only "articles" and "notes".

PUBMED (advanced search) and PsycINFO/PsychLit:

- ("behavi* therapy" OR "cognitive therapy" OR "cognitive behavio* therapy" OR "exposure therapy" OR "exposure treatment" OR "exposure session*" OR CBT OR "cognitive reest*" OR "anxiety manage*" OR flooding OR "systematic desens*")
- (anxiety OR phob* OR panic OR OCD OR obsess* OR PTSD OR "stress disorder*" OR GAD)
- (resist* OR refract* OR non-respons* OR non-respond* OR nonrespond* OR augment* OR "sequential treatment" OR "addition of CBT" OR "partial respond*" OR "crossover treatment*" OR "second-line treatment*" OR "second-line recommendation*" OR "fail to respond" OR "second level option*" OR "fail* to respond*" OR "fail* to fully respond*" OR "prior medication trial" OR non-remit* OR nonremit* OR "remain* sympt*")

The terms were searched directly in advanced search (All Fields) and the results of each individual search were combined. We used exactly the same strategy in PUBMED and PsycINFO/PsychLit.

Besides the searches in the online databases, manual searches were performed in the reference list of the articles reviewed and times cited lists (Base ISI). Experts on the field were consulted too for additional existing studies that might have not been identified.

### 2.2. Inclusion criteria

We included only "articles" and "notes"; review articles, book chapters and dissertations were excluded. Studies that used psychotherapeutic techniques other than CBT were excluded. We focused on CBT because it is one of the most extensively researched forms of psychotherapy (Butler et al., 2006) being the most investigated psychotherapeutic intervention for anxiety disorder. We included all types of traditional CBT, as can be seen by the terms used in our search strategy (i.e. cognitive therapy, behavior therapy, exposure therapy, flooding, anxiety managing, cognitive restructuring, cognitive behavior therapy). We excluded studies that employed the term "resistance" with a different meaning (i.e. that did not focus on resistance to pharmacological treatment), because we wanted to have a homogeneous sample. We also included studies that investigated patients with co-morbid psychopathological conditions. Case reports with 10 or fewer cases were excluded, as they represent a major methodological limitation according to the criteria for case series set by Pincus et al. (1993). Studies of CBT as a next-step strategy for pharmacological treatment resistant patients were found only for the three anxiety disorders, namely PTSD, OCD, and panic disorder. Fig. 1 shows the study selection process. Table 1 shows the selected studies.

## 3. Results

Our search found 603 papers, which were reviewed to identify our final sample of 17 articles (see Fig. 1). Of the selected studies, eight were randomized controlled trials, one was an open controlled trial, six were open, non-controlled trials, two were naturalistic trials, and one was a case series. The results from the selected studies were sorted by primary disorder and all diagnoses were defined according to the

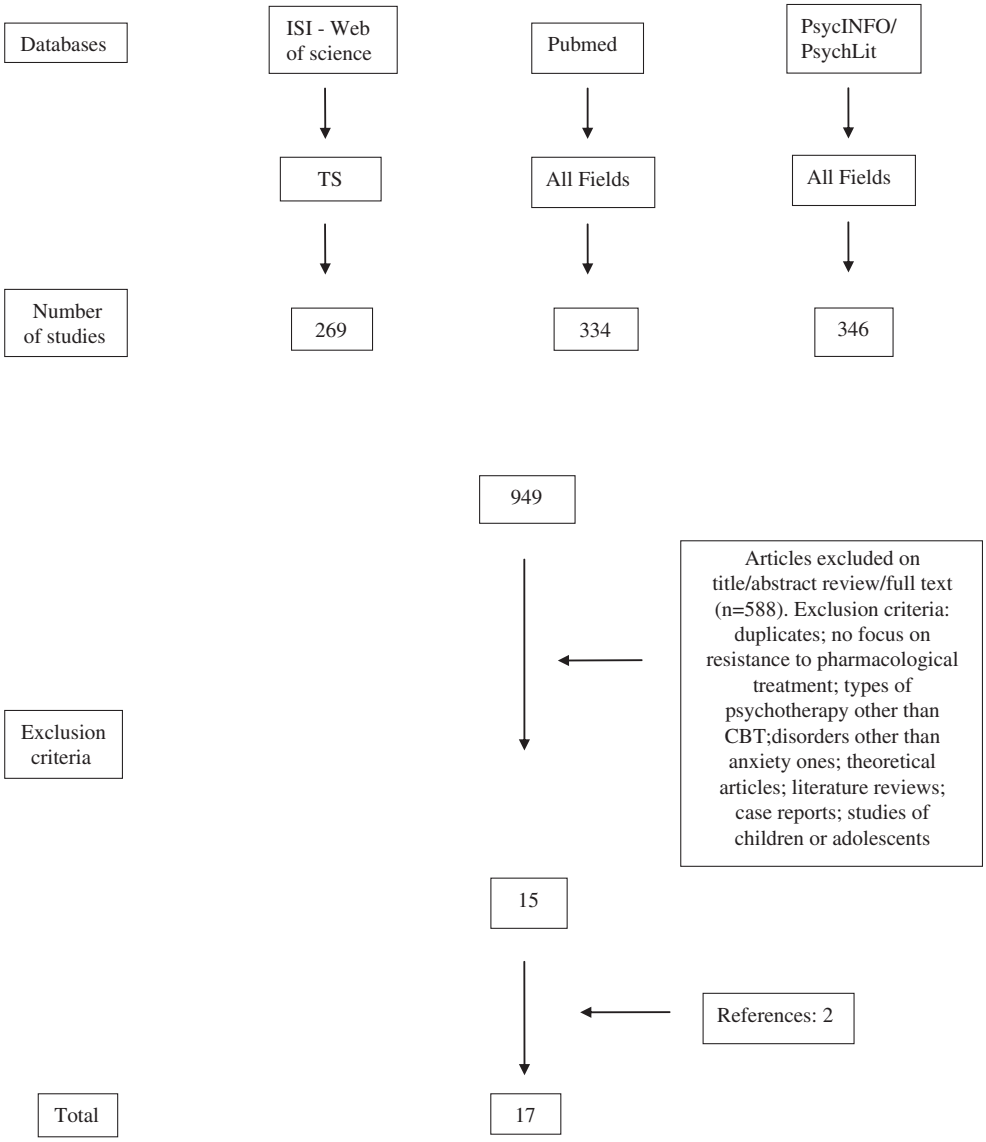


**Fig. 1.** Summary of the study selection process.

diagnostic criteria of the *DSM-IV*, with the exception of a study by Pollack et al. (1994), in which the criteria were defined by the *DSM-III*. All of the identified studies reported the efficacy of CBT as a next-step strategy for patients with residual symptoms, despite pharmacological treatment refractory to initial pharmacotherapy.

### 3.1. Studies with post-traumatic stress disorder (PTSD)

We identified four randomized controlled studies and they all indicated that the addition of CBT to pharmacotherapy for PTSD and related symptoms was associated with further clinical improvement, with significantly lower scores at the assessment with the measures used. All selected studies were conducted with Cambodian or Vietnamese refugees and, thus, CBT protocols had to be culturally adapted. The techniques included information about a cognitive-behavioral model of PTSD and panic disorder, muscle relaxation and diaphragmatic breathing, cognitive restructuring, and interoceptive and imaginary exposure.

Hinton et al. (2005) randomized 40 patients with PTSD and comorbid neck-focused and orthostasis-cued panic attacks refractory to initial pharmacotherapy for initial and delayed CBT treatment. Resistance was defined as the presence of PTSD despite receiving supportive counseling and an adequate trial of an SSRI (selective serotonin reuptake inhibitor) (i.e. at least 1 year on the maximally tolerated dose). Twelve individual weekly CBT sessions were conducted and all patients continued supportive psychotherapeutic and pharmacological treatment (an SSRI combined with the benzodiazepine clonazepam). The immediate treatment group showed significantly lower scores, with large effect sizes for all outcome measures. The severity of

**Table 1**
Description of the included reviews.

| Study | *n* | Disorder | Study design | Criteria for resistance | CBT Protocol | Main outcome measures and results | |
|---|---|---|---|---|---|---|---|
| Hinton et al., 2005 | 40 | PTSD | Randomized controlled | PTSD, despite supportive counseling and SSRI for at least 1 year at the maximum tolerated dose | 12 weeks | Lower scores on the ASI, CAPS and SCL scales. 60% patients in remission | |
| Hinton et al., 2009 | 24 | PTSD | Randomized controlled | PTSD, despite supportive counseling and an adequate trial of an SSRI at the maximally tolerated dose for at least 6 months | 12 weekly sessions | Reduction in the CAPS score and in one physiologic measure. 60% in remission | |
| Hinton et al., 2004 | 12 | PTSD | Randomized controlled | PTSD, despite at least 1 year with an adequate dose of an SSRI and supportive counseling | 11 weekly sessions | Significant main effects for time occurred for ASI, HTQ and HSCL | |
| Otto et al., 2003 | 10 | PTSD | Randomized controlled | Failure to respond adequately to clonazepam treatment combined with an adequate dose of SSRI other than sertraline | 10 sessions | Reduction in CAPS, HSCL and ASI scores. Medium to large effect sizes for PTSD and associated symptoms | |
| Simon et al., 2009 | 46 | PD | Randomized controlled | Failure to meet remission criteria (no panic attacks for at least 1 week and a CGI-S score ≥ one) | 12 weekly sessions | Reduction on the PDSS, CGI-S, HARS and ASI scores. There were no significant differences between the "medication optimization" and CBT groups. 10% in remission | |
| Heldt et al., 2006b | 63 | PD | Open non-controlled | Residual symptoms of PD, despite an adequate dose of antidepressants in the previous 4 months | CBGT for 12 weeks | Reduction in CGI-S, PI and HAM-A scores. 81% had no panic attacks and 64% in remission | |
| Heldt et al., 2006a | 32 | PD | Open non-controlled | Residual symptoms of PD, despite an adequate dose of an antidepressant in the previous 4 months | CBGT for 12 sessions along 4 months | Decrease in CGI and HAM-A scores. Clinical improvement in 50% of patients for agoraphobia, 47% for anticipatory anxiety, and 38% for HAM-A anxiety symptoms. 75% had no regular panic attacks and 44% patients in remission | |
| Pollack et al., 1994 | 15 | PD | Open non-controlled | Residual symptoms of PD, despite at least 3 months of adequate pharmacotherapy and CGI score ≥ 3 | CBGT for 12 weeks | Reduction in CGI-S score. 47% panic-free patients and 53% panic-free at follow-up. 40% in remission | |
| Otto et al., 1999 | 24 | PD | Open clinical case series | CGI ≥ 4 and at least 2 months of treatment with any tricyclic antidepressant at the prescribed dose | CBGT for 12 sessions | Decrease in CGI-S and PDSS scores. 60% of the 'adequately-treated' patients and 43% of the 'inadequately-treated' ones in remission | |
| Tenneij et al., 2005 | 96 | OCD | Randomized controlled | Response to 3 months of pharmacotherapy (reduction of at least 25% in Y-BOCS) | Cognitive therapy for 6 months | Reduction in Y-BOCS score, but not for the HAM-A. Significant increase in anxiety symptoms | |
| Simpson et al., 2008 | 94 | OCD | Randomized controlled | OCD for at least 1 year, Y-BOCS total score ≥ 16 and some improvement with an SSRI administered for at least 12 weeks before CBT | 17 sessions of each modality of CBT, twice a week | Improvements in Y-BOCS and HAM-A scores. 74% achieved responder status. 33% achieved minimal symptoms | |
| Tolin et al., 2007 | 41 | OCD | Randomized controlled | Chronic symptoms of OCD (at least for 1 year) and at least moderate severity (total Y-BOCS score ≥ 16, along with a CGI score ≥ 4) | 15 sessions, twice a week | Decrease in the Y-BOCS and CGI-S scores. 65% of the patients were considered to be responders | |
| Tundo et al., 2007 | 21 | OCD | Naturalistic | Y-BOCS score ≥ 16, despite at least one adequate SSRI | 4 sessions per month during 4 months | 19% reduction in Y-BOCS score, and 16% in CGI-S | Significant improvements in Y-BOCS and CGI-S. Increased awareness of OCD symptoms and improvement in the general functioning |
| Tundo et al. 2009 | 24 | OCD | Naturalistic | Y-BOCS score ≥ 16 | 12 months | 67% was rated as "much improved" or "very much improved" (CGI-S) and 25% had a Y-BOCS total score of ≤ 16 | |
| Tolin et al., 2004 | 15 | OCD | Open controlled | At least moderate OCD (Y-BOCS score ≥ 16), symptoms duration for more than 1 year, and inadequate response to at least two adequate trials with an SSRI | 15 sessions, from 1 to 5 times a week | 39.5% decrease in Y-BOCS score and 66.6% of patients improved on the CGI | |

**Table 1** *(continued)*

| Study | *n* | Disorder | Study design | Criteria for resistance | CBT Protocol | Main outcome measures and results |
|---|---|---|---|---|---|---|
| Kampman et al., 2002 | 9 | OCD | Open non-controlled | Y-BOCS reduction of less than 25% | 12 sessions | 41% reduction rate in Y-BOCS score, 32.6% symptom reduction on the HDRS and 43% for the HARS |
| Simpson et al., 1999 | 5 | OCD | Open non-controlled | Y-BOCS score ≥ 16, despite an adequate dose of an SSRI for at least 12 weeks | 17 sessions, 2 times a week | 49% mean decrease in Y-BOCS score. Improvement on HAM-D and CGI-S scores |

PD = panic disorder; CBGT = cognitive behavioral group therapy; CGI-S = Clinical Global Impressions-Severity; PDSS = Panic Disorder Severity Scale; OCD = obsessive–compulsive disorder; Y-BOCS = Yale-Brown Obsessive Compulsive Scale; SSRI = selective serotonin reuptake inhibitor; PTSD = posttraumatic stress disorder; ASI = Anxiety Sensitivity Index; CAPS = Clinician-Administered PTSD Scale; SCL = Symptom Checklist 90-R subscales; HTQ = Harvard Trauma Questionnaire; HSCL = Hopkins Symptom Checklist; SCL = Symptom Checklist-90-R; HAM-A = Hamilton Anxiety; PI = Panic Inventory; PDSS = Panic Disorder Severity Scale; HARS = Hamilton Anxiety Rating Scale; HDRS = Hamilton Depression Rating Scale.

both types of panic and flashbacks improved across the treatment. Twelve patients (60%) of the immediate treatment group and 10 (50%) patients of the delayed treatment group did not meet the criteria for PTSD anymore. No difference was found across the groups in the outcome measures at the last evaluation (after the waiting group received CBT), and at the 12-week follow-up.

In a recent study, which included psychophysiological measures evaluation, 24 Cambodian refugees with PTSD and co-morbid orthostatic panic attacks were randomized for initial and delayed CBT treatment [Hinton et al. (2009)]. Resistance was defined as the presence of PTSD symptoms despite supportive counseling and maximally tolerated dosage of an SSRI for at least 6 months. The CBT protocol also consisted of 12 weekly sessions and all patients continued receiving supportive psychotherapy and medication (SSRI and/or benzodiazepine) during the study. Patients randomized for immediate CBT had significant improvements in all psychometric measures and in one physiologic measure (systolic blood pressure response to orthostasis). Patients in the waiting group showed improvements too after receiving CBT.

In a small study by Hinton et al. (2004), 12 traumatized Vietnamese refugees with PTSD and panic attacks were randomized for initial and delayed culturally adapted CBT treatment. Resistance was defined as the presence of PTSD despite treatment with an SSRI at an adequate dose for at least 1 year and supportive counseling. Eleven weekly individual sessions of CBT focusing on PTSD and comorbid panic attacks were held and all patients remained on the usual medications (for the most part, a combination of one SSRI, one benzodiazepine, and gabapentin). Significant main effects for time occurred for all psychometric outcome measures.

Otto et al. (2003), in a pilot study, randomized 10 Cambodian female refugees for treatment with either sertraline alone or combined sertraline plus 10 sessions of CBT. Pharmacotherapy-refractory or nonresponsive patients were defined by the failure to respond adequately to clonazepam treatment combined with an adequate dose of an SSRI other than sertraline. Combined treatment over SSRI-treatment alone was associated with better changes in psychometric measures and provided additional gains in the range of medium to large effect sizes for PTSD and associated symptoms.

### 3.2. Studies with panic disorder

We identified one controlled randomized study, three open studies and one case series evaluating the efficacy of CBT as an additional treatment for patients with panic disorder who were medication-resistant. All five studies, which included techniques such as providing information on the cognitive-behavioral model of panic disorder, diaphragmatic breathing, muscle relaxation, cognitive restructuring, interoceptive exposure, in vivo exposure, situational exposure and relapse prevention, consistently supported the efficacy of CBT.

Simon et al. (2009) had 46 patients who failed to meet remission criteria randomized to a 24-week treatment comprising three stages: (a) a 6-week lead-in with open-label sertraline flexibly dosed up to 100 mg (or an equivalent dosage of escitalopram) to prospectively define treatment refractoriness ($n = 39$); (b) patients who did not meet remission criteria by the sixth week were randomized in a double-blind fashion for 6 weeks of increased-dose SSRI versus continued SSRI plus placebo ($n = 24$); and (c) patients were randomized for 12 weeks to added CBT or "medication optimization" with SSRI and clonazepam ($n = 19$). Twelve weekly 50-minute individual CBT sessions were held for a total of 12 weeks. Remission status was defined as no panic attacks for at least 1 week and a Clinical Global Impression-Severity (CGI-S) (Guy, 1976) score of 1 or 2. In the first stage, 8 (20.5%) of the patients remitted. In the second stage, increasing the SSRI dose did not result in greater improvement or remission rates. In the third stage, both augmentation with CBT and "medication optimization" were associated with significant reduction in panic disorder and associated symptoms. However, there was no significant difference between groups. Only one patient in each group achieved remission and there was no significant difference between the groups, and the effect sizes were all small. At the naturalistic 3-month follow-up, 6 (35%) of the 17 patients remitted, 3 from the CBT group and 3 from the "medication optimization" group.

In the open trial conducted by Heldt et al. (2006), 63 patients with panic disorder and agoraphobia who were nonresponders to pharmacotherapy received 12 sessions of group CBT along 4 months. Thirty-two patients took part in a previous study (Heldt et al, 2003). All patients were using medication for panic disorder during CBT. The patients included were those with residual symptoms of panic disorder (panic attacks, anticipatory anxiety and phobic avoidance) despite a stable dosage of medication for at least 4 months and CGI-S score ≥ 3. Improvement was defined by at least 50% reduction in the Hamilton Rating Scale for Anxiety (HAM-A) (Hamilton, 1959), agoraphobia, and anticipatory anxiety scales. Remission was defined as absence of panic attacks and CGI-S score ≤ 2 in

the last 2 months of follow-up. After CBT, there was a significant reduction in symptoms for all measures (frequency of panic attacks, agoraphobia and anticipatory anxiety), with maintenance of gains at 1 year follow-up. Fully 51 patients (81%) had no panic attacks and 40 (64%) met remission criteria (no panic attacks and CGI-S score ≤ 2). Twenty-eight patients (43%) were not in psychiatric treatment during the follow-up period. Roughly two-thirds of the patients remitted in the follow-up period and the gains were maintained despite medication reductions.

Heldt et al. (2006) found that brief cognitive behavior group therapy was effective in improving panic disorder patients' quality of life. Thirty-two patients who were pharmacotherapy-refractory were treated with 12 sessions of CBT during 4 months. Patients considered refractory had residual symptoms of panic disorder despite a previous pharmacological treatment with an adequate dose of an antidepressant lasting at least 4 months. All patients had been on pharmacological treatment for a long period (mean = 4 years). Improvement was defined as a reduction ≥ 50% on the PI (Panic Inventory) and HAM-A. Remission was defined as absence of panic attacks and CGI ≤ 2. Significant improvements were found in all domains of quality of life, which was associated with decreases in general and anticipatory anxiety and in agoraphobic avoidance. Symptoms of anticipatory anxiety had a more significant impact on the quality of life of the patients than the panic episodes themselves. At the end of the treatment, clinical improvement occurred in 16 (50%) patients for agoraphobia, 15 (47%) for anticipatory anxiety, and 12 (38%) for HAM-A anxiety symptoms. Twenty-four patients (75%) had no regular panic attacks and 14 (44%) patients remitted (CGI-S score ≤ 2 and no panic attack).

Pollack et al. (1994) reported that significant benefits resulted from the addition of CBT to the treatment of patients with panic disorder and agoraphobia who presented incomplete response to pharmacological treatment. Fifteen patients (eight were considered relatively refractory since they received an inadequate dose of medication and seven were deemed refractory because they remained symptomatic despite having received an adequate dose) were treated with cognitive behavior group therapy during 12 weeks. Incomplete response to the pharmacological treatment was defined by the presence, despite at least 3 months of pharmacological treatment, of residual symptoms of panic attacks that were severe enough to interfere with functioning. The study included patients without panic attacks (with CGI-S score ≥ 3), patients who did not receive an adequate dose of medication and patients who received an adequate dose of medication (in accordance with established doses) There was a significant reduction in the CGI-S, in the frequency of panic attacks, increase in the number of patients without panic attacks (from 5 to 7), and attainment of remission in 6 patients (CGI-S ≤ 2). The gains were maintained at the 2 month follow-up.

In the case series reported by Otto et al. (1999), patients refractory to an adequate dose of medication were selected as 'adequately-treated' nonresponders ($n = 10$) and 'inadequately-treated' nonresponders ($n = 14$), i.e. patients refractory to an inadequate dose of medication. The criteria for 'adequately-treated' were: at least 2 months of treatment with any tricyclic antidepressant at a dose ≥ 150 mg/day, fluoxetine at a dose ≥ 20 mg/day, sertraline at a dose ≥ 50 mg/day, paroxetine ≥ 40 mg/day, nefazadone at a dose ≥ 300 mg/day, phenelzine at a dose ≥ 45 mg/day, alprazolam ≥ 4 mg/day or clonazepam at a dose ≥ 2 mg/day. Many patients were taking more than one medication. The criteria for resistance also included current CGI-S ≥ 4. Twelve sessions of cognitive behavior group therapy were held. Both groups showed significant decrease in CGI-S and PDSS (Panic Severity Scale) scores. Sixty percent of the 'adequately-treated' patients and 43% of the 'inadequately-treated' ones met remission criteria (a CGI-S score of 1 or 2). Effect sizes tended to be greater for 'adequately-treated' patients, although *t*-test comparisons between improvements in each group did not show any significant differences.

### 3.3. Studies with obsessive-compulsive disorder (OCD)

We found three randomized controlled trials, three non-controlled open studies and two naturalistic trials; all of them reported gains from the addition of CBT to the treatment of patients with OCD which exhibited residual symptoms despite pharmacological treatment. In all these trials, CBT treatment focused on exposure and response prevention.

Tenneiji et al. (2005) reported that CBT brought additional benefits to patients who responded to drug therapy. Ninety-six patients who responded to 3 months of pharmacotherapy (reduction of at least 25% in Y-BOCS) were randomized to 18 sessions of additional CBT or to continuation with drug therapy alone for 6 months. All patients were treated with fixed doses of 300 mg/day of venlafaxine or 60 mg/day of paroxetine for 12 weeks. Patients with HAM-D (Hamilton Depression Rating Scale) (Hamilton, 1960) score > 16 were excluded. Remission was defined as a total Y-BOCS (Goodman et al., 1989) score ≤ 8. Patients in the medication alone group were submitted, 6 months later, to CBT for another 6 months and did not present a significant decline in the Y-BOCS score. Patients who received additional CBT obtained better results in the Y-BOCS and attained remission more frequently than those which remained on medication only. The results suggest that the outcomes are better when CBT is added immediately after drug treatment.

In a controlled randomized trial, Simpson et al. (2008) compared CBT with two other treatment modalities—exposure and response prevention ($n = 48$) and training of stress management skills ($n = 46$)—as strategies to enhance the effects of pharmacological treatment with SSRI in OCD patients. Patients had OCD for at least 1 year, Y-BOCS total score was ≥ 16, and some improvement had to be observed with an SSRI administered at an adequate dose for at least 12 weeks before the beginning of the study. Other medications could be used as long as the SSRI had been at a stable level for at least 4 weeks and remained so along the study period. A total of 17 sessions of each CBT modality were held twice a week. The exposure and response prevention group obtained a significantly greater reduction in the obsessive–compulsive symptoms and in the Y-BOCS, Obsessive-Compulsive Inventory and in the HAM-A scores. There was no difference between the groups in the other measures: HAM-D, Social Adjustment Scale and Quality of Life Enjoyment and Satisfaction Questionnaire. A significantly larger number of patients who received exposure and response prevention remained with residual symptoms.

Tolin et al. (2007) randomized 41 patients for self- or therapist-administered exposure and response prevention. All patients were currently using or had already received an adequate trial of an SSRI medication. The determination of what constitutes an adequate medication trial was based on published guidelines and consultation with OCD researchers. In order to be adequate, the medication had to be maintained at the indicated dose for OCD for at least 10 weeks. Other inclusion criteria were: having chronic symptoms of OCD (at least for 1 year) and at least moderate severity, defined as a total Y-BOCS score ≥16, along with a CGI score ≥4 ("moderately ill"). Therapist-administered exposure and response prevention comprised 15 sessions twice a week for 7 weeks and a half. In self-administered exposure and response prevention, patients were told to follow the instructions in a book for 6 weeks. In the cases with prior medication trials, as there were no pre-medication records, the patients were asked to report if they had subjectively experienced no more than a minimum effect of medications. Patients were instructed not to make changes to the medication during treatment and at the 1-, 3- and 6-month follow-ups. There was a significant statistical and clinical reduction in symptoms for all patients. However, among patients who had received therapist-administered exposure and response prevention there was a noticeably larger reduction of the OCD symptoms and a much higher proportion of responders. After treatment, 65% of the patients who received therapist-administered exposure and response prevention were considered to be responders while only 25% of those who received self-administered exposure and response prevention were considered so. At the final follow-up, these proportions were 50% and 25%, respectively.

The naturalistic trial by Tundo et al. (2007) provides further evidence for the effectiveness of CBT as an additional treatment for real-world, medication-resistant nonresponder OCD patients. Patients who had OCD for at least 1 year and did not respond to at least one adequate SSRI trial were selected. Patients were considered nonresponders at the end of the pharmacological treatment if they still met the criteria for OCD and had Y-BOCS total score ≥16. Twenty-one patients completed the treatment with CBT, which consisted of four sessions per month during the first 4 months and then continued with one to four sessions per month. The length of CBT was not established and the pharmacological treatment was not modified during CBT. Statistically significant improvements in Y-BOCS and CGI-S scores were found after the beginning of CBT and at the 1-year follow-up. Four patients had Y-BOCS scores ≤16. There was a slight reduction in OCD symptoms and improvements in patients' insight and general functioning.

Another naturalistic trial by Tundo et al. (2009) investigated the effectiveness of 12 months of CBT using exposure and ritual prevention in association with serotonin reuptake inhibitor (SRI) for pharmacotherapy treatment-resistant patients. Patients who have had OCD for at the least 1 year were included and were nonresponders (Y-BOCS ≥ 16) to al least one adequate trial of SRI. Pharmacotherapy treatment was not changed during the trial period. Statistically significant improvements in Y-BOCS and CGI-S scores were found at follow-up. Patients were considered responders if they were rated "much improved" of "very much improved" on the CGI-S. From 24 patients who completed the treatment, 16 (67%) were rated as "much improved" or "very much improved" and 6 (25%) had a Y-BOCS total score of ≤16.

In another study (Tolin et al., 2004), 15 patients who presented inadequate response to pharmacotherapy at adequate dose, after remaining 1 month in waiting list, received 15 sessions of CBT, from 1 to 5 times a week. The patients had at least moderate OCD (as measured by the Y-BOCS scores ≥ 16), symptoms duration ≥ 1 year, and at least two adequate trials with an SSRI. The determination of adequate medication was based on published guidelines and guidance from OCD researchers. The patients had several comorbidities and were in general characterized by poor insight and putting low effort into CBT, factors that are predictors of poor response. OCD severity (as measured by Y-BOCS) decreased significantly after CBT and the gains were maintained at the 6-month follow-up. One participant did not participate in the 1-month follow-up but returned for the 3-month one. Another patient did not participate in the 3-month follow-up but returned for the 6-month one.

Kampman et al. (2002) investigated the effects of adding CBT to an ongoing treatment with fluoxetine in patients with OCD who were nonresponders to fluoxetine alone. Nine females with OCD symptoms for at least 1 year and Y-BOCS score of at least 16 (or 10 for patients with obsessions only) completed the study. Patients who had previously used an adequate dosage of an SSRI or been submitted to CBT were excluded. The patients were submitted to a 2–6 week waiting period to wash out the usual medications before beginning the study. Treatment was divided in two phases: (a) patients received fluoxetine 60 mg/day for 12 weeks and (b) patients who had a Y-BOCS reduction of less than 25% and were classified as nonresponders received 12 sessions of CBT in addition to the ongoing treatment with fluoxetine. After CBT, OCD symptoms were reduced in 7 of the 9 patients. There was a reduction in OCD symptoms (Y-BOCS) of 8.5% in the first phase and 41% in the second. The general anxiety and depression symptoms diminished as well. There were statistically significant differences between Y-BOCS scores in the first and in the second phases of the treatment, showing a decrease in OCD symptoms in both phases and in general anxiety in phase two.

Simpson et al. (1999) also found benefits from the addition of CBT in 5 patients with residual symptoms (Y-BOCS score of ≥16) despite an adequate trial with an SSRI for at least 12 weeks. Besides the medication, 5 patients completed 17 sessions of CBT twice weekly. The patients had a diagnosis of OCD for at least 1 year and had experienced some improvement (verbal self-report) with adequate dosage and duration of an SSRI treatment. Adequate SSRI dosage was defined as: clomipramine, ≥225 mg/day; fluoxetine, ≥60 mg/day; paroxetine, ≥60 mg/day; sertraline, ≥200 mg/day; and fluvoxamine, 250 mg/day. Among other reasons, patients were excluded if they had received CBT with exposure and response prevention for OCD and were using a psychoactive drug other than an SSRI. Blood drug levels were also checked before and after CBT in order to ensure the maintenance of the prescribed medication. There was no change to blood drug levels in most patients during exposure and response prevention, which suggests the link between improvements and therapy. No patient stopped medication. Follow-ups were performed at 1, 2, 3, 4, 5, 6, 9 and

12 months. There was a significant benefit after exposure and response prevention in all psycometric measures used.

## 4. Discussion

### 4.1. Findings

The most important result of this systematic review is that all studies suggest the efficacy of CBT as a next-step strategy for treating patients with anxiety symptoms who do not remit with pharmacological therapy only. However, of the 17 studies selected here only 8 are randomized controlled trials and all had small samples, which is a significant limitation in the field. Thus, performing further randomized controlled trials in resistant patients would be important to provide further evidence of the efficacy of CBT for this population. In PTSD, differently from other disorders, the quality of available evidence is stronger: despite the limited number of conducted studies, all four identified here were randomized controlled trials.

It is important to note that among all anxiety disorders, we could only found studies about CBT as a next-step strategy for pharmacotherapy resistant for OCD ($n=8$), panic disorder ($n=5$), and PTSD ($n=4$). Despite the high prevalence, morbidity and treatment-resistance rates of anxiety disorders like social anxiety disorder and generalized anxiety disorder (GAD), there is a lack of studies in these fields. Actually, there is evidence that this scarcity of studies in social anxiety and GAD is not confined to the theme of next-step strategy in pharmacological treatment resistance. Concerning social anxiety disorder, Crippa (2009) showed a smaller number of studies than for other anxiety disorders. Possible causes include the little attention from the media to social anxiety disorder and the fact that many patients remain undiagnosed and under-treated. The lack of studies in the fields of social anxiety disorder and GAD was also noted in the bibliometric analysis by Boschen et al. (2007), in which the anxiety disorders with the greatest number of publications in the 1980–2005 period were PTSD, panic disorder and OCD. The growing number of publications in PTSD is dominant in this period, this being the anxiety disorder with the highest number of publications since 1980. Boschen et al. (2007) showed that in the 2005–2015 period, the publications on anxiety disorders will continue to be dominated by PTSD, panic disorder and OCD.

### 4.2. Quality of included studies

We found a lack of standardization in treatment protocols, terminology and definitions used in the reviewed studies. Each study follows a particular CBT protocol, with marked differences regarding, for instance, the length of treatment, CBT techniques and treatment format (individual or group). The terminology for describing non-remission or resistance to pharmacotherapy varied widely too, with use of such different names as resistance, refractory, “not respond”, “incompletely responsive”, nonresponder and “failure to respond”.

Some studies did not define remission at all and failed to assess it as a potential improvement measure [Hinton et al. (2009), Hinton et al. (2004), (Otto et al. 2003), Simpson et al. (2008), Tolin et al. (2007), Tundo et al. (2007), Tolin et al. (2004), Kampman et al. (2002)], while others defined remission through changes to the psychometric measures and absence of clinical symptoms [Heldt et al. (2006), Pollack et al. (1994), Simon et al. (2009), Tundo et al (2007), Hinton et al. (2005) & Heldt et al. (2006)]. The studies also varied regarding the number of patients who achieved remission. In Heldt et al. (2006), 40 (64%) patients presented criteria for remission. In Otto et al. (1999), 60% of the ‘adequately-treated’ patients and 43% of the ‘inadequately-treated’ patients presented remission. In Tundo et al (2007), only 4 of the 21 patients with TOC remitted. In Hinton et al. (2005), 12 (60%) patients with PTSD remitted. It should be noted that the criteria for remission were more clearly defined and the remission rates were higher for studies in panic disorder. Therefore, even first-line treatments such as pharmacotherapy and CBT were found to face limitations when the percentage of patients who achieves total remission is considered. Our study highlights the importance of creating a standardized operational definition of resistance, since the diversity of definitions of resistance severely limits the ecological validity of the findings.

We noticed that CBT for PTSD had to be adapted to the cross-cultural characteristics of the sample. All of the patients with PTSD were Cambodian or Vietnamese refugees, with high levels of resistance to pharmacotherapy and severe, complex symptoms due to the several repeated, prolonged traumas. We highlight the importance of the positive results obtained with this sample of patients with specific cultural features in which the protocols were culturally adapted and showed good results.

Other limitations are the reduced number of studies with follow-up evaluation data as well as their relatively brief duration (2–12 months). Out of the 16 selected studies, only eight showed follow-up data: one in PTSD with a 3-month follow-up (Hinton et al., 2005); three in panic disorder, one of which with a 1-year follow-up (Heldt et al, 2006), another with 3-month follow-up (Simon et al., 2009) and another with 2-month follow-up (Pollack et al., 1994); and finally four studies in OCD, of which one had a 1-year follow-up (Tundo et al, 2007), two with 1-, 3- and 6-month follow-up (Tolin et al., 2004 & Tolin et al., 2007), and one with 1-, 2- 3-, 4-, 5-, 6-, 9- and 12-month follow-up (Simpson et al., 1999).

Another methodological issue of the reviewed studies concerns the multiple co-morbidities found. Most of the patients had a clinically relevant secondary diagnosis, for the most part depression and other anxiety disorders, which not only hindered patient response to CBT intervention for a given anxiety disorder but also made the analysis of the results and the comparisons across group more complex. Moreover, anxiety disorders vary widely in their presentations and outcomes obtained with CBT. It is important to emphasize the positive results found in all trials on the efficacy of CBT in patients with residual symptoms and multiple co-morbidities, which represents patients typically found in treatment settings.

Studies also differ concerning the variability of results and the outcome measures used. Some studies used very specific measures and other more global measures, but none used blind assessment of outcome. Furthermore, all studies included psychometric evaluations, but only one trial with

PTSD patients (Hinton et al., 2009) included psychophysiological measures (systolic blood pressure, diastolic blood pressure and heart rate) as additional parameters for assessment of treatment outcomes. The use of such measures, less prone to the kind of bias often associated with the use of self-reporting scales, such as over- or under-reporting of symptoms, is growing, with potentially relevant implications for the development of more individualized and successful treatment modalities.

### 4.3. Limitations

Some limitations of the present review include the choice of only two electronic databases, albeit the most important ones, and the possibility of overestimation of positive response about the efficacy of CBT, as there is a trend of omitting studies reporting negative results. Moreover, inasmuch as this is a qualitative systematic review, it has some inherent methodological limitations that can be addressed only through quantitative evaluations, a feature that hinders a more accurate evaluation of the efficacy of CBT.

Although all studies indicated that additional benefits can be obtained through the addition of CBT, our results are limited by the fact that we found only eight studies with sound research designs. The take-home message from this systematic review is that more research is necessary to guide the next-step interventions as well as the replication of the findings of the studies in larger samples of patients, with more sophisticated controlled studies, including double-blind evaluation, psychotherapy placebos, and longer follow-up data (Smits & Hofmann, 2008).

### 4.4. Recommendation

We recommend the development of more randomized controlled studies with larger samples of patients to add evidence of the efficacy of CBT. In particular, social anxiety disorder and GAD are poorly explored research areas, with a demand for future studies, due to the small number of publications and the absence of works investigating CBT as a next-step strategy.

As many of the selected studies do not show long-term data, performing studies with longer follow-ups to demonstrate the maintenance of gains from CBT represents, too, an important area with demand for future investigations.

Because the studies used different words to express the concepts of resistance and remission, we recommend a standardization of these concepts taking into account the specificities of each anxiety disorder.

We observed the need for better summarization of the main outcomes of the studies. For instance, several authors could present their results in a more data focused way (e.g., given the % in remission, etc.).

We also propose, for future research works, studies on pharmacotherapy as a next-step strategy for CBT. In the present review we found few studies with this purpose (Baetz, M. & Bowen, R. C., 1998; Hoffart et al., 1993; Kampman et al., 2002; Hofmann et al., 2006; Kushner et al., 2007; Shim et al., 2008; Simon et al., 2008) which represents a field with relevant studies, in view of the importance of developing next-step strategies for patients who do not remit despite established efficacious, first-line treatments.

Even with the use of next-step strategy and the positive reports of efficacy, there is a room for improvement in CBT interventions among patients treated with drugs, since a substantial number of patients did not present remission.

**Conflict of interest**

There is no actual or potential conflict of interest including any financial, personal or other relationships with other people or organizations within three (3) years of beginning the work submitted that could inappropriately influence, or be perceived to influence, their work.

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