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Predictors of relapse and recurrence following cognitive behavioural therapy for anxiety-related disorders: A systematic review

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Abstract

Cognitive behavioural therapy (CBT) is an effective psychological treatment for anxiety-related disorders (anxiety disorders, post-traumatic stress disorder, and obsessive-compulsive disorder). However, relapse of anxiety symptoms is common following completion of treatment. This study aimed to identify predictors of relapse of anxiety after CBT for adult (18+) patients to enable the identification of 'at-risk' patients who could potentially benefit from relapse prevention interventions. A systematic review and meta-analysis was conducted, including studies found in PsycINFO, PubMed, Scopus, and Web of Science, and through hand-searches of references lists and reverse citations. Nine studies met eligibility criteria (N=532 patients). On average, 23.8% of patients experienced relapse following completion of CBT. A total of 21 predictors were identified and grouped into seven categories: residual symptoms; personality disorders; medication; clinical features; stressful life-events; degree of improvement; and demographics. A meta-analysis of residual symptoms as a predictor of relapse yielded a moderate but non-significant pooled effect size (r=0.35; 95% CI -0.21, 0.74, p = .08). Further research with adequately powered samples and standardised operationalisations of relapse are required to identify robust predictors.

Keywords: Anxiety; Cognitive behavioural therapy; CBT; Recurrence; Relapse

Introduction

Depression and anxiety-related disorders, including post-traumatic stress disorder (PTSD) and obsessive-compulsive disorder (OCD), are the most common mental health problems worldwide. The World Health Organization (WHO; 2017) estimated that more than 300 million people suffer from depression globally, with a similar number suffering from an anxiety disorder. According to WHO (2017), depression is the largest contributor to global disability, and anxiety disorders are ranked as the sixth largest contributor. This considerable impact is partly due to depression and anxiety having high rates of relapse and recurrence (Hardeveld, Spijker, De Graaf, Nolen & Beekman, 2010; Verliet, Craske & Hermans, 2013). For example, anxiety disorders have been estimated to have recurrence rates ranging from 39-56% following treatment (Bruce et al., 2005; Vervliet et al., 2013). Relapse is defined as the clinically significant re-emergence of symptoms within 12 months of remission being achieved, while a recurrence is defined as the re-occurrence of a disorder after 12 months of remission (Bockting, Hollon, Jarrett, Kuyken & Dobson, 2015). For simplicity, we will be referring to both definitions as 'relapse', as the literature often group relapse and recurrence cases into the same group.

Cognitive-behavioural therapy (CBT) is an effective intervention for depression and anxiety problems, and has been demonstrated to have superior longer term outcomes compared to pharmacological treatment (Cuijpers et al., 2013a; Hollon, Stewart & Strunk, 2006; Otto, Smits & Reese, 2005). A recent systematic review of 69 randomised controlled trials found that CBT for anxiety-related disorders was associated with significantly lower levels of anxiety symptoms compared with control conditions 12 months after treatment completion (van Dis et al., 2019). However, only six of these trials reported relapse rates, with the majority of trials assessing long-term outcomes by aggregating means of symptom severity ratings at follow-up. This process unfortunately masks within-individual change, thus preventing the rate of patients

that have experienced a clinically significant increase in symptoms (i.e., relapsed) from being understood.

Indeed, studies that have assessed long-term outcomes by exploring relapse rates have demonstrated it is relatively common following CBT. For example, White et al. (2013) estimated that approximately 18% of patients with panic disorder, who completed and responded to CBT and did not receive any relapse prevention intervention, relapsed within 21 months. Furthermore, relapse has a significant detrimental impact on healthcare costs, leading to service inefficiencies, due to a 'revolving door' process whereby patients return for further treatment (Roscoe, 2019). Therefore, there is a humanitarian and health economic need to better understand how to improve the longer-term outcomes of CBT.

A recent systematic review and meta-analysis attempted to address this knowledge gap by reviewing the current literature on predictors of depression relapse following CBT (Wojnarowski, Firth, Finegan & Delgadillo, 2019). This review calculated a pooled relapse rate for depression of 33.4% across 13 studies, and also found consistent support for two predictors of depressive relapse: the presence of residual depressive symptoms, and prior episodes of depression. However, little is known regarding what factors are associated with relapse following CBT for common mental health problems other than depression. Gaining a better understanding of factors that predict relapse of anxiety symptoms could enable psychological services to offer targeted relapse prevention interventions, such as mindfulness-based cognitive therapy (MBCT; Segal, Williams & Teasdale, 2002) or continuation-phase CBT (White et al., 2013).

To address this gap in the literature, we reviewed the contemporary literature on predictors of relapse of anxiety-related disorders following CBT. This review aimed to estimate

the prevalence of relapse events and to identify predictors of relapse using systematic review and meta-analytic methods.

Method

Protocol and registration

The systematic review protocol was prospectively registered and published in the international Prospective Register of Systematic Reviews (PROSPERO) database (Protocol ID: CRD42019133033).

Eligibility criteria

To be included in this review, studies must have (1) included an adult (18+) sample of patients who had been diagnosed with an anxiety disorder, PTSD, and/or OCD, and (2) who had completed a course of CBT with remission of symptoms as identified by validated measures and/or diagnostic interviews. Co-morbidity of other mental health disorders was allowed, but the primary disorder must have been an anxiety-related disorder. The review also only included (3) longitudinal cohort studies or randomised controlled trials that had been (4) published in the English language (5) in peer-reviewed journals, and that (6) included a follow-up period of at least twelve weeks and (7) investigated at least one potential predictor of relapse.

As this review aimed to improve understanding of risk factors associated with relapse following acute-phase CBT, studies were excluded if any formal maintenance intervention designed to prevent relapse (e.g. booster sessions) had occurred. This was to ensure that any identified predictors of relapse are associated with the delivery of CBT, and not with the

delivery of maintenance interventions. However, studies that did not control for participants receiving additional, external therapy during follow-up (i.e., not provided as part of the study) were included. Considering that services and trials cannot disallow participants from seeking additional psychological support, these studies were included for three reasons: (1) to allow for a wider synthesis of the literature; (2) greater external validity, as this situation likely reflects best what occurs in routine practice; and (3) to enable an assessment of the extent to which studies did not control for this factor. There were no exclusion criteria associated with medication use, however studies that introduced pharmacological treatment as a maintenance intervention were excluded.

Search strategy

Four databases (PsycINFO, PubMed, Scopus, and Web of Science) were searched for relevant articles published between January 1990 and May 2019, using a predetermined search strategy (Supplementary Materials A). This strategy consisted of variations of the keywords: 'cognitive behavioural therapy'; 'relapse'; 'predict'; and variations of each of the investigated disorders ('separation anxiety disorder', 'selective mutism', 'specific phobia', 'social anxiety disorder', 'panic disorder', 'agoraphobia', 'generalised anxiety disorder', 'PTSD', and 'OCD').

Study selection

The search strategy identified 233 unique records. After screening of titles and abstracts by a single reviewer, 208 ineligible studies were excluded. Following this, two reviewers independently assessed the full-texts of the remaining 25 articles and, both agreed only four of these articles were eligible for the review. The most common reasons for exclusion were:

different treatments being grouped together for analysis; inclusion of a maintenance intervention; and the lack of a relapse outcome measure. Reference lists of the four eligible articles were also hand-searched, and new studies that cited the eligible articles were searched in Web of Science. This step identified four additional eligible articles. Finally, one other eligible article was identified outside of the systematic search process. Therefore, a total of nine eligible articles were included in this review. The corresponding authors of these eligible articles were contacted by e-mail to request further references that may be eligible, but this did not produce any additional eligible articles. A PRISMA diagram (Moher, Liberati, Tetzlaff, Altman & The PRISMA Group, 2009) summarising the selection process is illustrated in Figure 1.

[Figure 1]

Quality assessment

Two reviewers independently assessed the quality and risk of bias of the nine eligible articles, using an adapted[1] version of the CASP Cohort Study Checklist (Critical Appraisal Skills Programme, 2018). Interrater agreement for the two reviewers' assessments was found to be fair (Cohen's kappa = 0.34), thus demonstrating significant disagreement between the reviewers in terms of their initial quality assessments. However, these disagreements were resolved through discussion, with reviewers reaching complete consensus on all items.

[1] The third section of the checklist (i.e. Section C – 'Will the results help locally?') was not used for this review, as it was not considered relevant to the review's objective.

Data extraction and synthesis

Data were extracted and tabulated by one reviewer using a structured form developed with guidance from the Cochrane Collaboration Data Collection Form (Cochrane Collaboration, 2014). A narrative synthesis of the characteristics, methods and results of the identified studies was conducted. If the investigation of an individual potential predictor was replicated across multiple studies and there was sufficient reporting of statistical information, a random-effects meta-analysis was also conducted to enable a quantitative synthesis of data. This was performed using the 'Meta-Essentials' Excel workbook for meta-analysis (Suurmond, van Rhee & Hak, 2017). To enable meta-analysis and the calculation of a pooled effect size, relevant inferential statistics (e.g. t-test, chi-square, log rank) were transformed into correlation coefficients (*r*). Heterogeneity was assessed using the Q and I^2 statistics (Higgins, Thompson, Deeks & Altman, 2003), while potential publication bias was examined through investigation of funnel plots using Egger's regression and rank-correlation tests. The small number of eligible studies prevented subgroup or moderator analyses from being possible.

Results

Study characteristics

The nine studies deemed eligible for review are described in Table 1, with all of the studies being longitudinal cohort studies. The mean age of participants within each study ranged from 30.6 to 42.4 years. Two pairs of studies were related. Braga, Manfro, Niederauer, and Cordioli (2010) was an investigation that continued on from Braga et al. (2005), and therefore used the same sample. Meanwhile, Fava, Zielezny, Savron, and Grandi (1995) was a preliminary investigation that preceded Fava et al. (2001a), and therefore used a sample that was later a subset of the latter article.

[Table 1 near here]

Panic disorder was the most commonly investigated disorder (*n*=4 studies). For the remaining five studies, two investigated OCD, two investigated social anxiety disorder, and one investigated a mix of anxiety disorders. No studies specifically examined separation anxiety disorder, selective mutism, specific phobia, generalised anxiety disorder, or PTSD. There was also variation in terms of the CBT interventions investigated; three studies explored relapse after one-to-one CBT, three following cognitive behavioural group therapy (CBGT), and three following exposure therapy. No studies reported using a treatment fidelity check or therapist competency measures. Moreover, one study exploring one-to-one CBT (Lincoln et al., 2005), used a relatively idiosyncratic treatment protocol. This protocol consisted of a five-to-seven-day intensive treatment phase consisting of high-density exposure with cognitive restructuring. Following this, participants were instructed to continue exposure in their everyday lives for six weeks, and were provided with further support from their therapist during this time if needed. The authors acknowledged that their adopted "format of treatment differed from existing approaches" (p. 212), with CBT for common mental health problems typically being delivered through weekly sessions (Arch et al., 2012; Cuijpers, Huibers, Ebert, Koole & Andersson, 2013b).

Relapse definitions

There were differences in how relapse was operationalised. Five studies assessed relapse status using the clinical global impressions scale (CGI; Guy, 1976). This scale assesses a clinician's subjective perception of the global severity of a disorder based on interview, and

ranges from 1-7 (minimal to severe symptoms). DiMauro et al. (2013b) used the CGI, but in contrast to other studies, used a self-report version. For every study that used the CGI, patients had to have a score greater than two ("borderline ill") to meet criteria for relapse. However, only one study (Otto, Pollack & Sabatino, 1996) used this as the only criterion for relapse; other studies had additional criteria in their outcome assessments, and these varied across studies (see Table 1).

There were two definitions of relapse that did not use the CGI. One was used in Fava et al.'s (1995, 2001a, 2001b) studies where relapse was defined as the return of panic disorder or social anxiety disorder as defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM[2]). Meanwhile, Lincoln et al. (2005) was the only study to assess relapse by calculating reliable change indexes (RCI), which is a psychometric criterion that assesses whether a change over time of an individual score is statistically significant and not a reflection of measurement error (Jacobson & Truax, 1991).

Follow-up

There was considerable variation in the length of follow-up periods, with there being a range of 1-14 years. Five of the nine studies had relatively brief follow-up periods that did not exceed 24 months. The three studies conducted by Fava et al. (1995, 2001a, 2001b) had median follow-up durations of four, eight, and six years respectively. These were median durations, as each of the three studies did not have standardised follow-ups, but instead had a range of follow-up durations. DiMauro, Domingues, Fernandez, and Tolin (2013b) reported that patients were followed-up one year after treatment, but a later corrigendum corrected this error

[2] Fava et al. (1995) used the revised, third edition of the DSM (American Psychiatric Association [APA], 1987), while Fava et al. (2001a, 2001b) used the fourth edition (APA, 1994).

by reporting that follow-ups occurred one-year post-treatment for only 37% of patients (DiMauro, Domingues, Fernandez & Tolin, 2013a). In fact, 33% of follow-ups occurred two-years post-treatment, and 30% occurred between three- and six-years post-treatment. Variability in follow-up durations may have impacted upon relapse rates, as there is increased opportunity for relapse events to occur with longer follow-ups. However, the three Fava et al. studies and Di Mauro et al (2013b) had four of the five lowest relapse rates of the included studies.

It is important to note that Heldt et al. (2011) only investigated relapse events that occurred in the second year of a two-year follow-up period, and therefore relapse events that occurred in the first year post-treatment were not considered. A previous study of the same sample (Heldt et al., 2006) investigated treatment response one-year after treatment completion, but did not consider relapse in this timeframe and therefore was not eligible for this review. An additional aspect of follow-up that varied across studies was whether or not some patients received additional, external therapy during the follow-up period. Only three of the nine studies (Fava et al., 1995[3], 2001a, 2001b) reported that no patients received additional therapy during this period, while four studies reported that some patients did receive additional therapy. The remaining two studies did not mention whether patients received further therapy post-treatment or not, with it not being possible to contact the corresponding authors of these studies for clarification.

Quality assessment

Seven of the nine studies were rated as "good", one was rated as "fair", and one was rated as "poor". Details about the ratings of individual studies can be found in Supplementary

[3] Although this was not explicitly stated in Fava et al. (1995), it was stated in Fava et al. (2001a).

Materials B. The two most common sources of bias across the nine studies were the failure to take into consideration in study design and/or analysis the potential confounding variable of patients receiving further treatment during follow-up, and consistent imprecision when reporting statistics.

Rates of relapse

Relapse rates ranged from 13% to 42%, with an average of 23.8% (*SD*=10.9%; excluding Otto et al., 1996, which did not report a relapse rate). OCD was the disorder with the highest relapse rate, with 35% relapsing within 12 months (Braga et al., 2005), and 42% experiencing a relapse/recurrence within 24 months (Braga et al., 2010). Social anxiety had the lowest relapse rate, with 13% relapsing at twelve months (Lincoln et al., 2005) and two to twelve years' follow-up (median=eight years; Fava et al., 2001b).

Predictors of relapse

The nine studies investigated a total of 147 variables as potential predictors of relapse, with 21 significant predictors ($p<0.05$) being identified (see Supplementary Materials C). These predictors can be grouped into seven categories: residual symptoms; personality disorders; medication; clinical features; stressful life-events; degree of improvement; and demographics. The majority of the results are discussed in narrative form. The 'residual symptoms' predictor was replicated across multiple studies and had sufficient statistical information for a quantitative synthesis.

Residual symptoms

The presence of residual symptoms of the primary disorder at the end of treatment was found to significantly predict relapse in a majority of studies (Braga et al., 2005; Braga et al., 2010; Fava et al., 1995; Fava et al., 2001a; Fava et al., 2001b; Heldt et al., 2011). In contrast to these studies, Lincoln et al. (2005) and DiMauro et al. (2013b) both found no significant effect of post-treatment levels of anxiety symptoms on relapse. However, the study by DiMauro et al. (2013b) had a particularly small sample consisting of only four relapse events, and this may explain the lack of a significant effect.

A meta-analysis was conducted to quantitatively synthesise the results of these studies. Five of the eight studies that investigated the predictive role of residual symptoms on relapse were included in the meta-analysis. Fava et al. (1995) and Braga et al. (2005) were excluded as these studies were associated with Fava et al. (2001a) and Braga et al. (2010) respectively, while DiMauro et al. (2013) was excluded as this study provided insufficient statistical information. The pooled effect estimated by the meta-analysis represented a moderate correlation between residual symptoms and relapse, however it was not found to be statistically significant (r=0.35 (95% CI -0.21, 0.74), p=0.08). There was evidence of considerable heterogeneity (Q=56.68, $p < 0.001$; I^2=92.94%), while regression (t=0.93, p=0.42) and rank correlation tests (Kendall's Tau=0.40, p=0.33) for funnel plot asymmetry suggested no evidence of likely publication bias. Given the small number of eligible studies that provided data for meta-analysis, no further sensitivity analyses were carried out.

Three studies also investigated residual symptoms of conditions different from the studies' primary target conditions as predictors of relapse. For example, Fava et al. (1995, 2001a, 2001b) and Lincoln et al. (2005) all investigated residual levels of depression as a potential predictor of relapse of panic disorder/social anxiety disorder. Moreover, as additional potential predictors of social anxiety disorder relapse, Fava et al. (2001b) investigated residual generalised anxiety and somatic anxiety, while Lincoln et al. (2005) investigated residual levels

of agoraphobia, obsessive-compulsiveness, and hypochondriasis. None of these variables were found to be significant predictors of relapse. This may potentially indicate that only residual symptoms of the primary target condition are predictive of relapse, however small sample sizes may also explain the lack of significant findings.

Personality disorders

Fava et al. (1995, 2001a) and Fava et al. (2001b) found that participants with a co-morbid personality disorder were significantly more likely to relapse. The presence of a personality disorder was also the strongest predictor identified in both studies. No other study investigated this variable as a predictor of relapse.

Medication

Post-treatment use of medication had mixed results as a predictor of relapse, with a total of four studies investigating its effect, and two observing a significant effect. Specifically, three studies examined the effects that post-treatment use of antidepressants had on relapse (Fava et al., 2001a, 2001b; Heldt et al., 2011), with only one finding it to be a significant predictor (Fava et al., 2001a). Similarly, the same three studies investigated post-treatment use of benzodiazepines as a potential predictor, with two finding a significant effect (Fava et al., 2001a, 2001b). A different study, conducted by Otto et al. (1996), did not separate the two forms of medication in their analyses, instead investigating post-treatment use of antidepressants and/or benzodiazepines as a single predictor of relapse. Although they initially found a significant effect, this became non-significant ($p>0.05$) when accounting for the additional variable of agoraphobic subtype.

Clinical features

Three different clinical features were found to be significant predictors of relapse in one study each. The first was baseline severity of disorder, which was found by Otto et al. (1996) to significantly predict panic disorder relapse. However, this effect was not replicated by other studies (Braga et al., 2005; Di Mauro et al., 2013; Fava et al., 1995; Fava et al., 2001a; Fava et al., 2001b; Heldt et al., 2011; Lincoln et al., 2005). The second feature found to be a significant predictor of relapse was initial levels of depressed mood (Fava et al., 2001a). However, this effect was not observed by two different studies (Fava et al., 2001b; Lincoln et al., 2005), with co-morbid depression also not being a significant predictor in two other studies (Heldt et al., 2011; Otto et al., 1996). The final clinical feature was having a specific subtype of a disorder. Lincoln et al. (2005) found that patients with social anxiety disorder who relapsed reported a more generalised subtype of the disorder (i.e. experienced fear towards a greater range of social situations) at baseline compared to patients who remained in remission. Furthermore, Otto et al. (1996) found that patients who had panic disorder with the agoraphobic subtype were significantly more likely to relapse. In contrast however, Heldt et al. (2011) found that baseline severity of agoraphobia did not predict relapse.

Degree of improvement

Braga et al. (2005) found that patients with OCD who had a larger reduction in symptom severity were less likely to relapse than patients who achieved less intense improvement. This finding was not replicated by DiMauro et al. (2013b) in a study investigating patients with a range of anxiety disorders. However, the small sample size of this study (n=4 relapse cases) may explain the lack of a significant finding.

Stressful life-events

Only one study, conducted by Heldt et al. (2011), explored the role of stressful life-events on relapse. They found that the experience of a stressful life-event characterised by "conflict" (i.e., interpersonal relationship difficulties, or occupational or financial problems) during a two-year follow-up period was a significant predictor of a relapse that occurred in the second-year of the follow-up period. Stressful life-events characterised by "loss" (e.g., death of a loved one, divorce), "medical illness" (i.e., onset or exacerbation of medical condition), or "other" (i.e., events that could not be categorised into the other three groups) did not predict relapse. However, more participants had experienced a "conflict" event (n=17) than a "loss" event (n=6), "medical" event (n=7), or "other" event (n=12), and this relatively larger subsample may have increased the opportunity of an effect to be identified.

Demographics

Age was the only demographic predictor to be found significant by any study, with younger participants suffering from panic disorder with agoraphobia being more likely to relapse (Fava et al., 2001a). Lincoln et al. (2005) also reported that younger patients with social anxiety disorder were more likely to relapse than older patients. However, this difference was no longer significant when the additional predictor of generalised subtype was taken into consideration. Indeed, age was found to be a non-significant predictor in three other studies (Fava et al., 2001b; Heldt et al., 2011; Otto et al., 1996). Other demographic variables investigated but not found to be significant were: gender, marital status, education; social class; and employment.

Discussion

This is the first study to systematically review the literature on predictors of relapse in anxiety-related disorders following completion of CBT. As such, this provides complementary evidence to the review by Wojnarowski et al. (2019), which specifically examined depression relapse following CBT. The pooled relapse rates found were similar (33.4% for depression; 23.8% for anxiety reviewed in this study). Overall, this demonstrates the high rates of relapse associated with common mental health disorders. Strict inclusion criteria were created and followed, identifying only those studies that investigated the durability of acute-phase CBT not augmented with maintenance interventions designed to prevent relapse (e.g. booster sessions, MBCT). This criterion was followed to ensure that any predictors of relapse could be confidently associated with the delivery of CBT, and not with the role played by maintenance interventions.

The strict inclusion criteria were defined *a priori* however, and this resulted in only nine studies being identified as eligible. Only one variable investigated as a potential predictor of relapse was consistently supported as being significant in more than two studies: residual symptoms related to the primary disorder. This variable was a significant predictor of relapse in four studies, and non-significant in two studies. However, one of these two studies was the only study rated as having poor methodological quality and only involved four relapse cases in their analyses. A meta-analysis subsequently estimated a moderate positive correlation between residual symptoms and relapse, although this was not statistically significant (p=0.08). This was potentially due to the analysis only involving five studies, and indeed this precluded more detailed sensitivity analyses to examine potential sources of heterogeneity. Wojnarowski et al.'s (2019) meta-analysis of predictors of relapse of depression also identified residual symptoms to be an important predictor of relapse (Wojnarowski et al., 2019). In fact, the pooled effect size was highly similar across both reviews (r=0.34 for depression; r=0.35 for anxiety).

This indicates that the presence of residual symptoms is currently emerging as a risk factor of relapse across common mental health problems. Paykel (2008) suggested that residual symptoms were a predictor of relapse as they represent the persistence of the original disorder, albeit in a milder presentation. However, understanding as to why residual symptoms appear to predict relapse remains limited.

Despite this review only identifying one replicated predictor of relapse, other potential predictors were identified. For example, the presence of a personality disorder was only investigated by two studies, but was found to be the strongest predictor in both. This further highlights the limited research into the impact of co-morbid personality disorders on the outcomes of CBT, and psychological therapies more generally. Indeed, none of the studies reviewed by Wojnarowski et al. (2019) investigated the presence of personality disorders as a potential predictor. Furthermore, a recent scoping review investigating the effectiveness of psychological therapies at treating patients with depression and/or anxiety who have co-morbid personality disorders concluded that there is a dearth of research in this area, and that no firm conclusions can be drawn (French, Turner, Dawson & Moran, 2017). Clearly, more research is required to understand the influence the presence of personality disorders have on CBT outcomes for patients with common mental health problems.

Another potential predictor identified by this review is the degree of improvement patients experience over the course of treatment, with larger symptom improvement appearing to be protective against relapse. This was a significant predictor in one study, and although the only other study to investigate this variable did not find it to significantly predict relapse, this other study was assessed as being of "poor" quality and only explored four relapse cases. Smaller symptomatic improvement may be predictive of relapse for similar reasons as those posited by Paykel (2008) in relation to residual symptoms, with it potentially representing a

relatively diminished responsiveness to treatment, and the consequent persistence of the disorder in a milder form.

Finally, a third variable that holds promise in the prediction of relapse is occurrence of a stressful life-event during the post-treatment follow-up phase. Only one study investigated this variable, and only one form of stressful event (i.e., an event characterised by "conflict" vs "loss", "medical", or "other") was found to be significant. However, it is possible sample constraints limited the opportunity for the other forms of stressful events to be identified as significant predictors. The systematic review on predictors of depressive relapse similarly identified only one study that investigated the occurrence of stressful life events during follow-up as a predictor, and this study also found a significant effect (Harkness, Theriault, Stewart & Bagby, 2014; Wojnarowski et al., 2019). Interestingly, Harkness et al. (2014) found that exposure to stressful events mediated the predictive relationship between residual symptoms and depressive relapse. This may potentially indicate an explanation, alternative to the one posited by Paykel (2008), as to why the presence of residual symptoms may predict relapse. In summary, although these variables should be considered with caution due to limited investigation, they hold promise as potential predictors of relapse for future research.

There were a number of limitations associated with the studies included in this review. For example, the studies may not have identified statistically significant predictors due to the small sample sizes across all of the studies. As shown in Table 1, sample sizes ranged from *n*=40-200, while the numbers of relapse cases ranged from *n*=4-31. These samples were highly likely to be underpowered to identify significant predictors that may have even a large effect on the risk of relapse. For example, Cohen's sample size estimate criteria (Cohen, 1992) suggests that for a comparison of means with a continuous predictor using ANOVA at least *n*=26 relapse cases would be required to detect a large effect size with 80% power. Similarly, *n*=64 relapse cases would be needed to detect a medium effect size, and *n*=393 cases for

identification of a small effect size. Out of the nine studies included in this review, only Fava et al. (2001a; *n*=31 relapse cases) had a sample large enough to detect a large effect size. However, even this study was not sufficiently powered to detect medium or small effect sizes. Furthermore, all other studies investigated a sample that included less than *n*=20 relapse cases. This is a major limitation of the studies included in this review.

One other potential reason why studies may not have consistently identified the same predictors to have a significant effect on the risk of relapse is the variety of relapse operationalisations used. As shown in Table 1, no two unique studies used the same measure for relapse, except for the studies conducted by Fava et al. (2001a, 2001b; reoccurrence of DSM disorder). This lack of consistency in definition likely had an effect on differences between studies in terms of relapse rates and identified significant predictors.

Another limitation that may explain the heterogeneity in results is that all of the reviewed studies were longitudinal cohort studies. Although these studies may allow for greater generalization of results as compared to randomised controlled trials, they also have less control of the therapeutic process and consequently of confounding factors. For example, none of the nine studies reported an assessment of CBT fidelity or therapist competency. It is thus not possible to know if the therapists in these studies adhered to CBT treatment protocols. Therefore, some studies may have had relatively poorly delivered therapy, and this may potentially have influenced the contrasts in results between studies.

An additional limitation that may be related to the prevalence of cohort studies in this review is that in some studies patients received further therapy during the follow-up period. Only two studies reported that no patients in their samples received additional therapy during follow-up (Fava et al., 2001a, 2001b). Four studies reported that some patients received additional treatment but did not account for this in their analysis, and three studies did not

mention whether or not patients received further treatment. This limits the certainty with which these studies findings can be applied to acute-phase CBT, as their findings may have been influenced by the potential confounding variable of patients receiving continuation-phase interventions that likely influenced the maintenance of remission. Therefore, it is important that future studies take this factor into account, by routinely recording what other interventions are being received by patients following CBT. Furthermore, this limitation, along with lack of assessments related to CBT fidelity and therapist competency, highlights the need for more trial-based designs for the investigation of relapse of anxiety, as such designs are particularly suited for controlling such confounding variables.

Limitations

There were also limitations related to the methods of this systematic review itself. For instance, no studies were identified that investigated relapse of separation anxiety disorder, selective mutism, specific phobia, generalised anxiety disorder, or PTSD. Furthermore, meta-analyses were planned for this review, however a quantitative synthesis was only possible for one investigated predictor. The small number of published articles, many predictors not being investigated in multiple studies, and a lack of sufficient reporting of statistical information prevented more meta-analyses from being possible. A narrative review was conducted instead for the remaining investigated variables, and the subjective nature of such a review is less ideal than a quantitative synthesis of results. The small number of eligible studies also did not allow for subgroup (e.g., results by intervention, primary disorder) or moderator analyses (e.g., patients receiving continuation-phase interventions). Finally, this review was also limited by the exclusions of grey literature and studies published in languages other than English.

Future research

Overall, this review has highlighted the limited research that exists regarding predictors of relapse of anxiety disorders, PTSD, and OCD. This is especially the case for separation anxiety disorder, selective mutism, specific phobia, generalised anxiety disorder, and PTSD, as no eligible studies that investigated relapse of these disorders were identified. The limited research in this area echoes the conclusions drawn by Wojnarowski et al. (2019) in their systematic review of predictors of relapse of depression. Clearly, there is currently a lack of understanding regarding relapse following CBT for both depression and anxiety. Further research that is adequately powered, alongside more trial-based designs, is urgently needed to address this gap in knowledge. Moreover, additional research is needed, particularly on the effect of residual anxiety symptoms on relapse, so that more robust meta-analyses can be conducted.

Many studies were considered ineligible for this review as they did not assess relapse as a follow-up outcome, despite being well-designed studies that assessed multiple predictors of long-term outcomes with complete and sufficiently long follow-up periods (e.g., Ogawa et al., 2010). As mentioned previously, many studies of CBT typically assess long-term treatment response using continuous measures of symptom severity, and do not use categorical measures of relapse. This process, which involves the aggregation of mean symptom severity ratings at the group-level, obscures within-individual change and prevents the identification of relapse rates, thus making it difficult to explore individual differences in the long-term maintenance of treatment gains. Therefore, it is important for future research that investigates the long-term outcomes of CBT to do so with a measurement of relapse.

However, it is also important future studies are designed using a standardised, valid, and robust definition of relapse to ensure findings can be compared across studies. We believe

there are concerns regarding the majority of the relapse definitions used in the studies in this review. For example, five of the nine studies used the CGI as a measure of relapse. Although this measure has been demonstrated to have concurrent validity and to be sensitive to change (Berk et al., 2008; Leon et al., 1993), it remains a subjective measure of a clinician's perception of a patient's current condition, that is based upon a comparison to other patients they have personally treated. This subjectivity raises concerns regarding the validity of this approach. Therefore, we propose an approach to assessing relapse that is similar to that used by Lincoln et al. (2005), which used validated self-report disorder-screening measures and the calculation of RCI. We recommend future research should classify a patient as having relapsed when: 1) their score on the validated measure increases above the measure's diagnostic cut-off; and 2) the increase represents a statistically reliable and clinically significant deterioration in the patient's condition (i.e., an increase greater than the measure's RCI; Jacobson & Truax, 1991).

Clinical implications

This review highlights the highly recurrent nature of anxiety, with an average of 23.8% of patients relapsing after CBT. Considering this, it is therefore important that relapse prevention is a valued and fundamental component of the treatment process, with the development of relapse prevention blueprints being a core component of treatment. Furthermore, it is important that relapse prevention interventions, such as continuation-phase CBT and MBCT, are offered to patients who have received clinically successful acute-phase CBT. These interventions are cost-effective, due to there no longer being a need to provide another course of CBT in the future (Scott, Palmer, Paykel, Teasdale & Hayhurst, 2003; Wojnarowski et al., 2019). With improved knowledge of which patients are vulnerable to relapse, maintenance interventions may be targeted towards 'at-risk' patients. The presence of

residual symptoms is emerging as a potential risk factor that could be used to target patients with increased vulnerability to relapse.

Conclusion

In summary, approximately one quarter of patients who received clinically effective CBT for anxiety-related disorders experienced a relapsed. Yet, despite this concerning statistic, knowledge regarding what factors cause or influence relapse remains limited, with little research having been conducted in this area. Nevertheless, this review has highlighted the potential importance of residual symptoms as a prognostic indicator for the relapse of anxiety, adding to previous research that has demonstrated its value in the prediction of depressive relapse. However, further research is required before residual symptoms can be established as a robust risk factor of relapse of anxiety-related disorders. Other potential predictors, which could also be fruitful targets for future research, have also been identified, including the presence of a personality disorder, the degree of treatment improvement, and the occurrence of stressful life events. Most importantly, further research with adequately powered samples, and standardised measures and definitions of relapse is required. This will enable more risk factors to be discovered and established, and facilitate the development of evidence-based maintenance interventions targeted at those patients at greatest risk of relapse.

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