

# Dismantling CBT for panic disorder: protocol for a component-level network meta-analysis

## Authors

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## Abstract

**Introduction:** Panic disorder (PD) is common in the general population, with a lifetime prevalence of 3.7% for PD without agoraphobia and 1.1% for PD with agoraphobia. In line with the National Institute for Health and Care Excellence (NICE) guidelines, in a recent Cochrane review with network meta-analysis ([Pompoli 2015](#)) we found that, among explored psychological therapies, Cognitive-Behavioral Therapy (CBT) showed the most favourable evidence for the treatment of this disorder. While based on the broadly defined cognitive-behavioral framework, CBT for panic disorder may consist of one or more of several distinct therapeutic components such as relaxation, breathing retraining, cognitive restructuring, interoceptive exposure and/or in vivo exposure. To date it is unclear whether any therapeutic component of CBT is more effective than the others.

The aim of this review is to establish whether a specific combination of CBT components is superior to other combinations for the treatment of panic disorder with or without agoraphobia in terms of short-term remission, short-term response and short-term tolerability.

**Methods and analyses:** In March 2015 we conducted a comprehensive and systematic search of all psychological therapies for panic disorder in order to identify relevant studies for a Cochrane review that is currently in editorial phase before publication ([Pompoli 2015](#)). For this review, we will update and re-assess these search results according to inclusion and exclusion criteria relevant to this review: namely, we will include RCTs comparing CBT-based psychological therapies among themselves or versus control interventions (no treatment, wait list, attention/psychological placebo). Eligible are studies comparing treatments that can be regarded as combinations of up to 12 predefined components (waiting component, placebo effect, psychological support, psychoeducation, breathing retraining, progressive/applied muscle relaxation, cognitive restructuring, interoceptive exposure, in vivo exposure, virtual reality exposure, third wave components, face-to-face setting).

We will perform a component-level Network Meta-Analysis (NMA), which is an adaptation of the standard NMA model and can be used to disentangle the treatment effects of the different components included in composite interventions. Using this model will allow us to estimate the relative effects of various components of CBT. In order to fit the model we will employ the additive treatment effects assumption, i.e. the total effect of each composite intervention will be assumed to be equal to the sum of the effects of the relevant components. We will report the most efficacious components, and provide a ranking in terms of efficacy.

**Ethics and dissemination:** No ethical issues are involved. We plan to publish the full paper with study results in a peer-reviewed journal. The study search and data analyses may be updated subsequently in order to ensure that results will remain updated and reliable.

**Protocol registration number:**

### **Strengths and limitations of this study**

#### ***Strengths***

- This is going to be the first comprehensive component network meta-analysis exploring psychotherapy for panic disorder.
- Our methodology will adhere to the Cochrane Collaboration's standards, in order to guarantee a comprehensive study search and evaluation. The details of this methodology, as well as the choice of the outcomes and the description of statistical methods, are predefined and fully described in this protocol in order to limit the risk of biasing the review process through post-hoc decisions.
- By applying the component NMA, this work will be one of the first systematic attempts to disentangle the effectiveness of components in a complex psychological intervention, and the first to explore this issue specifically regarding CBT for panic disorder. Therefore, this review may contribute to a more precise identification of the psychological therapy that should be offered as a first-line option to patients affected by this disorder.

#### ***Limitations***

- This is an aggregate data meta-analysis; thus, defects in the methodology and reporting of the original studies may influence the final results. Despite our efforts to guarantee a comprehensive search and retrieval of original studies, we cannot exclude the risk that relevant but unpublished studies will not be detected by the study search process: if such missing studies will not be missing at random, final results may be affected by publication bias.
- For this review we decided to limit the analyses to three dichotomous outcomes, that is short-term remission, short-term response and short-term tolerability. This decision takes into account the high complexity of the planned analyses and the relative lack of studies exploring long-term outcomes; however, the absence of continuous and long-term outcomes may reduce the clinical relevance of our results.

## Background

### Description of the condition

Panic disorder is an anxiety disorder characterized by the recurrence of unexpected panic attacks, in which an intense fear or intense discomfort, accompanied by a series of bodily and/or cognitive symptoms, develop abruptly, without an apparent external cause, and reach the peak intensity within a few minutes (APA 2013). In the general population, about one quarter of people suffering from panic disorder also have agoraphobia (Kessler 2006), which consists in anxiety about being in places or situations from which escape might be difficult or in which help may not be available in the event of developing panic-like symptoms or other incapacitating or embarrassing symptoms (APA 2013).

Panic disorder is common in the general population, with a life-time prevalence of 3.7% for PD without agoraphobia and 1.1% for PD with agoraphobia (Kessler 2006). In primary care settings panic syndromes have been reported to have a prevalence of around 10% (King 2008).

### Description of the intervention

The National Institute for Health and Clinical Excellence recommends three types of intervention in the care of individuals with panic disorder (NICE 2011). According to the NICE guidelines, the interventions for which there is evidence for the longest duration of effect are, in descending order, psychological therapy, pharmacological therapy (antidepressant medication) and self-help. Among various psychological therapies, NICE guidelines recommend the use of cognitive-behavioral psychotherapy (CBT). In line with NICE recommendations, in a recent Cochrane review and network meta-analysis (Pompoli 2015) we found that, among explored psychological therapies, CBT ranked as the most effective treatment.

CBT for panic disorder is usually administered according to the manuals of Clark 1986 and Barlow 2000. In its classical form, CBT consists of various therapeutic components, mainly represented by psychoeducation, breathing retraining, muscle relaxation, cognitive restructuring, interoceptive exposure and in vivo exposure. Therefore, CBT combines elements of psychoeducation (PE), physiological therapies (PT), cognitive therapy (CT) and behavioral therapy (BT) in order to reduce emotional distress and psychological symptoms, assuming that cognitions, behaviours and emotions are interrelated.

In its new developments, commonly referred to as "third-wave CBTs" (3W), more importance is given to the form, rather than the content, of patients' thoughts. By focusing on the function of cognition, third wave therapies aim to help patients develop more adaptive emotional responses to situations. Some examples of 3W are represented by mindfulness-based cognitive therapy, acceptance and commitment therapy, compassionate mind training, extended behavioural activation, meta-cognitive therapy and schema therapy.

The above-mentioned psychological therapies can be administered within a classical face-to-face setting (either individual or group therapy) or through self-help means (books, computers, Internet, smart-phones). According to available evidence, there is no proof that an individual therapy is more effective than a group therapy (Pompoli

2015), nor that a face-to-face setting necessarily leads to better results than a self-help therapy administering the same therapeutic components (Cuijpers 2010).

In a component-level perspective, each of the above-mentioned psychological therapies can be conceptualised as a combination of one or more therapeutic components (see Types of interventions) each targeting different aspects of the disorder.

It has been observed that some combinations of these components seem to lead to better results than their isolated administration (Sánchez-Meca 2010), suggesting the possible presence of an additive mechanism. The presence of a synergetic mechanism (Welton 2009, Mills 2012, Thorlund 2012) may also be hypothesized; however, detecting and quantifying such an interaction might prove infeasible, unless there is sufficient evidence for each component (Mills 2012).

### **Why it is important to do this review**

Although available evidence suggests that CBT should be the treatment of choice for panic disorder, it is still unclear which therapeutic component or combinations thereof are contributory. In fact, under the denomination of CBT, we can find therapies that consist of different sets of therapeutic components.

However, it seems reasonable to hypothesize that different components (and combinations) have different efficacies and, therefore, that a certain sub-set of components could yield the best results, to which the adjunct of the other components would add little or no benefit (or possibly even harm).

The aim of this review is, therefore, to establish if a specific combination of CBT components appears to be superior to other combinations, for the treatment of panic disorder with or without agoraphobia, in terms of remission, response and dropouts in the short-term. The results of this study may contribute to a more precise identification of the psychological therapy that should be offered as a first-line option to patients affected by this disorder.

### **Objectives**

To assess the comparative short-term efficacy and tolerability (in terms of remission, response and dropouts), of different CBT components, and combination of components, for the psychological treatment of panic disorder with or without agoraphobia in adults.

## **Methods**

### **Criteria for considering studies for this review**

#### ***Types of studies***

We will include randomized clinical trials (RCTs) that compare any of the interventions with or without a control arm. We will exclude quasi-randomised controlled trials (in which treatment assignment was decided through

methods such as alternate days of the week). We will include cluster-randomised trials. We will include cross-over randomised trials, but we will consider only results from the first randomisation period because we believe that the carry-over effect of CBT interventions would be important. We will include studies in which the replacement of dropouts is allowed as long as replacements are low in number (less than 15% of the final sample, as arbitrary threshold) and evenly distributed among treatment arms.

### ***Types of participants***

#### **Age range**

We will include patients, aged 18 years or older, of both sexes. Studies that include some participants under the age of 18 will be included as long as at least 80% of patients are aged 18 years or above or they present results grouped by age.

#### **Diagnosis**

We will include studies that have enlisted participants with a primary diagnosis of panic disorder with or without agoraphobia diagnosed according to any of the following criteria: Feighner criteria ([Feighner 1972](#)), Research Diagnostic Criteria ([Spitzer 1978](#)), DSM-III ([APA 1980](#)), DSM-III-R ([APA 1987](#)), DSM-IV ([APA 2000](#)), DSM-5 ([APA 2013](#)) or ICD-10 ([WHO 1992](#)). When ICD-10 or DSM-5 are used, in which panic disorder and agoraphobia are separately diagnosable, this review will focus on panic disorder comorbid with or without agoraphobia. The latter decision was taken in order to be concordant with the current body of literature, most of which used DSM-III-R or DSM-IV and little, if any, has used ICD-10 or DSM-5.

We will include studies focusing on agoraphobia, rather than panic disorder, if operationally diagnosed according to the above-named criteria and when it can be safely assumed that at least 30% of the participants are suffering from panic disorder, as we did in our previous Cochrane review ([Pompoli 2015](#)).

#### **Setting**

Participants must be outpatients at the time of enrolment.

#### **Previous treatment**

Both treatment-naive patients and patients who have already undergone some previous treatment (either psychological or pharmacological) will be included, as long as they satisfy the above mentioned inclusion criteria. However, we will exclude studies where all participants have shown resistance to previously administered psychological therapies.

#### **Comorbidities**

We will include studies where participants have other anxiety disorders (for example generalised anxiety disorder, specific phobias) or with subthreshold panic disorder if: 1) separate results for patients with panic disorder are reported and 2) randomisation is stratified by diagnosis in case the trial includes a small number of participants with panic disorder (arbitrary threshold set at 40).

We will include studies in which the participants have physical comorbidities. However, we will exclude studies that explicitly focus on panic disorder or agoraphobia among patients with a certain physical comorbidity.

We will exclude studies in which all participants had a concurrent primary diagnosis of Axis I or II disorders other than panic disorder or agoraphobia.

### ***Types of interventions***

For the purposes of this review, we will include a psychological therapy or a control condition as long as it can be regarded as a combination of the following 12 components:

1. waiting component (*w*): participants are aware that they will receive an active treatment after a waiting phase. Usually patients on a wait list do not receive any sort of treatment during the waiting phase. However, in some trials patients allocated to the waiting list control condition receive some non-specific therapeutic components such as psychological placebo, psychoeducation or supportive psychotherapy while waiting. In such cases, we will consider the “waiting component” (*w*) as treatment defining.
2. placebo effect (*p/l*): effect of an intervention due to the patients’ belief that they are receiving some form of treatment.
3. psychological support (*ps*): effect of an intervention due to various non-specific techniques (e.g. encouragement, rationalizing and reframing, anticipatory guidance, etc.) administered within the context of a therapeutic alliance (Winston 2004)
4. psychoeducation (*pe*): it relies on providing patients information about their psychological disease. It can be explained to patients that their symptoms can be interpreted under certain psychopathological models that can vary across the different psychological approaches.
5. breathing retraining (*br*): it consists in teaching patients techniques aimed at correcting those respiratory patterns thought to elicit or sustain panic attacks.
6. progressive/applied muscle relaxation (*mr*): *Progressive muscle relaxation* is aimed at reducing general tension and achieving a body state that lowers the risk for stressors to provoke a panic attack (Bernstein 1973). In the so-called *applied relaxation* (Ost 1987), relaxation training and exposure are combined.
7. cognitive restructuring (*cr*): it can be defined as a psychotherapeutic process of learning to identify and modify irrational or maladaptive thoughts using strategies such as Socratic questioning, thought recording and guided imagery.
8. interoceptive exposure (*ine*): it consists in graded exposure to the body sensations which accompany panic
9. in vivo exposure (*ive*): it consists in graded exposure to real-life situations perceived as threatening
10. virtual reality exposure (*vre*): it consists in graded exposure to virtual reality simulations reproducing real-life situations perceived as threatening
11. third wave components (*3w*): within this group we include various techniques aimed at helping patients to develop more adaptive emotional responses to situations, such as the ability to observe

symptomatic processes without overly identifying with them or without reacting to them in ways that cause further distress (Roemer 2008).

12. face-to-face setting (*ftf*): this component consists in the administration of therapeutic components in a face-to-face setting (rather than through self-help means)

A list of possible combinations of the above-mentioned components is presented in the following table, in order to clarify which psychological therapies and control conditions we will include and how we will conceptualize them in a component perspective.

**Table 1 Possible combinations of included components and their corresponding interventions**

Combinations of included components	Corresponding intervention
w ( $\pm$ pl $\pm$ pe $\pm$ ps $\pm$ ftf)	WL (wait list)
	NT (no treatment)
pl + ftf	APP (attention/psychological placebo)
pl + pe	SH-PE (self-help psychoeducation)
pl + pe + ftf	PE (face-to-face psychoeducation)
pl ( $\pm$ pe) + ps + ftf	SP (supportive psychotherapy)
pl ( $\pm$ pe $\pm$ ps) + br/mr	SH-PT (self-help physiological therapy)
pl ( $\pm$ pe $\pm$ ps) + br/mr + ftf	PT (face-to-face physiological therapy)
pl ( $\pm$ pe $\pm$ ps $\pm$ br $\pm$ mr) + ct	SH-CT (self-help cognitive therapy)
pl ( $\pm$ pe $\pm$ ps $\pm$ br $\pm$ mr) + ct + ftf	CT (face-to-face cognitive therapy)
pl ( $\pm$ pe $\pm$ ps $\pm$ br $\pm$ mr) + ine/ive/vre	SH-BT (self-help behavioral therapy)
pl ( $\pm$ pe $\pm$ ps $\pm$ br $\pm$ mr) + ine/ive/vre + ftf	BT (face-to-face behavioral therapy)
pl ( $\pm$ pe $\pm$ ps $\pm$ br $\pm$ mr) + ct + ine/ive/vre	SH-CBT (self-help cognitive-behavioral therapy)
pl ( $\pm$ pe $\pm$ ps $\pm$ br $\pm$ mr) + ct + ine/ive/vre + ftf	CBT (face-to-face cognitive-behavioral therapy)
pl ( $\pm$ pe $\pm$ ps $\pm$ br $\pm$ mr $\pm$ ct $\pm$ ine $\pm$ ive $\pm$ vre) + 3w	SH-3W (self-help <i>third wave</i> CBT)
pl ( $\pm$ pe $\pm$ ps $\pm$ br $\pm$ mr $\pm$ ct $\pm$ ine $\pm$ ive $\pm$ vre) + 3w + ftf	3W (face-to-face <i>third wave</i> CBT)
<b>Legend:</b>	
“+” means “and”	
“ $\pm$ ” means “with or without”	
“/” means “and/or”	

Therapies can be of any length so that we will accept those given in a single session. We will include both individual and group therapies. Therapies can be administered either face-to-face or in their self-help version (for example through books, computer programs or Internet). Remotely administered therapies (for example through telephone, video-conference) will be excluded, because how much *ftf* component is involved is not always evident in such therapies.

We will exclude psychotherapy-pharmacotherapy combination therapies, in which the pharmacotherapy constitutes a component of the experimental intervention of interest. However, we will include studies in which a pharmacological co-administration is allowed as long as there are no systematic differences in drug administration between the study arms.

We will exclude studies in which a pharmacological placebo is either co-administered or used as the sole control condition.

We will exclude any other psychological approach (such as psychodynamic psychotherapy, interpersonal therapy (IPT), eye movement desensitization and reprocessing (EMDR) and Morita therapy) on the grounds that they cannot be conceptualized as resulting from a combination of the included components.

We will exclude family therapy, couple therapy and other psychosocial interventions whose intervention focus is not the individual but rather the family system or couple as a whole.

In multi-arm trials, we will include the study if at least two arms meet our inclusion criteria and will exclude from the analyses the study arms which do not, if any.

### ***Types of outcome measures***

For this review we will explore three outcomes:

#### Primary outcome

- Remission of panic disorder with or without agoraphobia in the short term

#### Secondary outcomes

- Response of panic disorder with or without agoraphobia in the short term
- Dropouts for any reason in the short-term

*Short term* is intended as within six months from treatment commencement. When multiple time point measures in the short term are available, preference will be given to measures at approximately three months after treatment commencement.

*Remission* is intended as a dichotomous outcome expressing the number of patients who reached a satisfactory end state as defined by global judgment by the original investigators. Examples would be 'panic free' and 'no or minimal symptom' according to the Clinical Global Impression Severity Scale (CGI-S, [Guy 1976](#)), or scoring 5 or less on the Panic Disorder Severity Scale (PDSS) ([Furukawa 2009](#)).

*Response* is intended as a dichotomous outcome expressing the number of patients who had a substantial improvement from baseline as defined by the original investigators. Examples would be 'very much or much improved' according to the Clinical Global Impression (CGI) Change Scale ([Guy 1976](#)), more than 40% reduction in



the score of the Panic Disorder Severity Scale (PDSS) (Shear 1997), and more than 50% reduction in the Fear Questionnaire Agoraphobia Subscale (FQ-ag) (Marks 1979).

When more than one index of remission or response is reported, preference will be given to the most global measure (e.g. in the case of remission, 'high end state functioning' status is usually a more global index than 'panic free' status); when more than one index is available but measures are equally 'global', preference will be given according to the following criteria:

1. Panic Disorder Severity Scale (PDSS) > Panic and Agoraphobia Scale (PAS) > Anxiety Sensitivity Index Revised (ASI-R) > ASI > Agoraphobic Cognitions Questionnaire (ACQ) > Body Sensations Questionnaire (BSQ) > other scales specific for panic disorder;
2. Clinical Global Impression – Severity Scale (CGI-S) > Clinical Global Impression – Improvement Scale (CGI-I) > Global Assessment Scale (GAS) > Global Assessment of Functioning (GAF) > other global scales;
3. Fear Questionnaire – Agoraphobia subscale (FQ-ag) > FQ-global > Mobile Inventory for Agoraphobia – Avoidance Alone (MI-AAL) > MI-Avoidance Accompanied (MI-AAC) > other scales specific for agoraphobia only;
4. Panic frequency > panic severity > other scales specific for panic attacks only.

*Tolerability* will be measured indirectly via the dropout rate from the study.

### **Search methods for identification of studies**

In March 2015 we conducted a comprehensive and systematic search of all psychological therapies for panic disorder in order to identify relevant studies for a Cochrane review that is currently in editorial phase before publication (Pompoli 2015). For this review, we will update and re-assess these search results according to inclusion and exclusion criteria relevant to this review.

The main searches (March 2015) were conducted in the Cochrane Depression, Anxiety and Neurosis group (CCDAN) specialised register, which collates weekly updated searches of MEDLINE (1950-), EMBASE (1974-) and PsycINFO (1967-); quarterly searches of the Cochrane Central Register of Controlled Trials (CENTRAL) and review specific searches of additional databases. Reports of trials were sourced from international trials registers such as World Health Organization's trials portal (ICTRP), drug companies, handsearching of key journals, conference proceedings and other (non-Cochrane) systematic reviews and meta-analyses. See appendix 1 for detailed search strategy. Supplementary searches were conducted on PubMed (see appendix 2 for detailed search strategy) and on trial registries. Further supplementary searches included: the check of the reference lists of all included studies and relevant systematic reviews; the personal query to trialists and subject experts for the individuation of unpublished studies; the check of the citation index Web of Science; the search of the grey literature database OpenSIGLE. No language restrictions were applied in any search.

The updated search will be conducted on the Cochrane Central Register of Controlled Trials (CENTRAL) and on PubMed after protocol registration, using search strategies similar to those described for the main searches.

## Data collection and analysis

### ***Selection of studies***

At least two out of three review authors (AP, AT, HI) will examine the titles and abstracts of references identified by the electronic search strategies described above to check whether the study is likely to be relevant. Each potentially relevant study located in the search will then be obtained as a full article and independently assessed for inclusion by the same two review authors and, in the case of discordance, resolution will be sought by discussion. When disagreement cannot be solved by discussion, arbitration will be provided by a fourth author (TAF). Where it won't be possible to evaluate the study because of missing information, the study will be classified as 'Study awaiting assessment' until further information can be obtained. The reasons for the exclusion of trials will be reported in the 'Characteristics of excluded studies' table. Decisions made in the study selection process (along with number of references and studies, and reasons for exclusion of studies) will be presented in a PRISMA flow diagram.

### ***Data extraction and management***

At least two out of three review authors (AP, AT, HI) will use a structured Excel data collection form to independently extract the data from the included studies. Again, any disagreement in the data extraction process, including the determination of constituent components of interventions, will be resolved either by discussion or by consultation with a fourth member of the review team (TAF). If necessary, authors of studies will be contacted to obtain further clarification.

### ***Assessment of risk of bias in included studies***

At least two out of three review authors (AP, AT, HI) will independently assess the risk of bias of the included studies using a manual adapted from the tool described in the Cochrane Handbook for Systematic Reviews of Interventions ([Higgins 2011](#)). The following domains will be assessed at a study level:

- 1 Random sequence generation and allocation concealment (selection bias).
- 2 Therapist and researcher allegiance, treatment fidelity (performance bias).
- 3 Blinding of outcome assessor (detection bias).
- 4 Incomplete outcome data (attrition bias).
- 5 Selective outcome reporting (reporting bias).

### ***Measures of relative component effects***

We will measure the relative component effects for all outcomes with the odds ratio (OR) and its 95% credible interval (CrI).

### ***Unit of analysis issues***

### **Cluster-randomised trials**

In cluster-randomised trials, groups of individuals rather than individuals are randomised to different interventions (Higgins 2011). If we identify any cluster-randomised trial, we will extract data about the outcomes that account for the clustering effect (e.g. from multilevel models). If the original authors report the numbers of events per arm but no analyses accounting for clustering effects is available, we will attempt an approximate analysis by dividing the total randomized participants and the number of events by the design effect, as described in the Cochrane Handbook for Systematic Reviews of Interventions, section 16.3.4 (Higgins 2011).

### **Crossover trials**

Crossover trials are trials where all participants receive both the control and intervention treatment but in a different order. The major problem is a carry-over effect from the first phase to the second phase of the study, especially if the condition of interest is unstable (Elbourne 2002). As this is the case with panic disorder, randomised crossover studies will be eligible but only data up to the point of the first crossover will be used.

### **Dealing with missing data**

We will try to contact the study authors for all relevant missing data.

In the case of missing outcome data, when a remission index is not reported but the means and standard deviations on a panic disorder scale are available, we will calculate the number of remitted participants according to a validated imputation method (Furukawa 2005); we will choose the panic disorder scales to be used for imputation according to the hierarchy presented in section “types of outcome measures”.

### **Data synthesis**

#### **Component-level network meta-analysis**

In this study we aim to compare all components listed in Table 1 against each other for remission, response and dropouts in the short term. In order to do this we will employ an extension of the standard NMA model presented by Welton et al. (Welton 2009) fitted within a Bayesian framework. In this approach the effect of each composite intervention is dismantled after modeling the component-specific effects. We will employ the additive effects assumption, i.e. we will assume the total effect of each composite intervention to be equal to the sum of the relevant component effects.

For example, if we assume a two-arm study  $i$  comparing intervention  $X$  (comprising, say, components  $pl$  and  $pe$ ) versus intervention  $Y$  (comprising, say, components  $pl$  and  $ftf$ ), then, using the log-odds ratios as an effect measure, the random effects, component-level NMA model is written as follows:

$$\text{logit}(p_{i,j}) = \begin{cases} \mu_i & \text{for intervention } X \\ \mu_i + \delta_i & \text{for intervention } Y \end{cases} \quad (1)$$
$$\delta_i \sim \text{Normal}(d_Y - d_X, \tau^2),$$

where  $p_{i,j}$  denotes the probability of having an event in treatment arm  $j$  of study  $i$  and  $\tau$  the (common) heterogeneity parameter; see next paragraph for details. The additive treatment effects assumption will then be imposed after setting  $d_X = d_{pl} + d_{pe}$  and  $d_Y = d_{pl} + d_{ftf}$ . The target parameters  $d_c$ ,

$c = \{w, pl, pe, ps, br, mr, ct, ine, ive, vre, 3w, ftf\}$  need to be estimated and their identifiability depends on the types of studies and the arms they include. We will set the effect of the waiting list component equal to zero ( $d_w = 0$ ) so that all other component effects are relative to the waiting list component. For instance, if all studies include  $pl$  in all arms it would be impossible to estimate  $d_{pl}$ . In addition, if two (or more) components are found to be always administered together in the included studies, it will not be feasible to assess their effects individually. In such cases we will estimate their joint effect.

We will report the odds ratios  $\exp(d_c)$  and 95% credible intervals for the relative effects between components. To rank the various components in terms of each outcome, while taking into account the uncertainty in treatment effects we will use the surface under the cumulative ranking curve (SUCRA) and the mean ranks (Salanti 2011).

One possible complication that we might need to tackle in our analysis is that, in order for this model to be able to disentangle the relative effects of the various components, it is necessary to have enough studies comparing a variety of combinations of components. Depending on the actual data (number of included studies and distribution of components across them), the model might not have enough power to draw any useful conclusion. If that is the case we will group components together in a clinically meaningful manner. More specifically, we will investigate whether estimation is improved by assuming common effects for breathing retraining ( $br$ ) and muscle relaxation ( $mr$ ), and also for interoceptive ( $ine$ ), in vivo ( $ive$ ) and virtual reality ( $vre$ ) exposure. If data allows, we will explore more advanced modeling options such as assuming exchangeable effects across similar components. We will assess the fit and parsimony of the various models using the deviance information criterion (DIC) (Spiegelhalter 2002). All models will account for correlations induced by multi-arm studies.

We will fit our model using OpenBUGS (Lunn 2009). We will use uninformative prior distributions for the treatment effects and for all coefficients in the meta-regression analyses we will perform, i.e.  $N(0, 100^2)$ . A minimally informative prior will be used for the heterogeneity parameter, i.e.  $U(0, 5)$  as well as an informative distribution (see below). For all analyses we will run multiple chains and we will evaluate the convergence of the model using the Brooks-Gelman-Rubin diagnostic.

### **Assessment of heterogeneity**

The estimation of comparison-specific heterogeneity parameters may be problematic when the network is scarcely connected or when there are few studies per comparison. Thus, an assumption commonly employed is to allow equal heterogeneity variances for all comparisons in the network (Higgins 1996). We denote this parameter by  $\tau^2$  in Equation (1) above. This assumption simplifies the fitting of the model and is especially valuable for the case that there are comparisons informed by few (or even only one) study in the network. If our network is scarce and estimation of heterogeneity is found to be problematic (e.g. very uncertain or the model does not converge) we will employ an empirical informative prior for heterogeneity as described by (Turner 2012) for semi-objective dichotomous outcomes. We will report the common  $\tau$  value along with 95% CrI.

### **Assessment of the transitivity assumption**

Standard NMA models generally rest on the assumption that effect modifiers have a similar distribution across treatment comparisons in the network ([Salanti 2012](#)). In the case of a component-level NMA this underlying assumption of the model is modified, so that instead of an intervention (which may be defined variably across studies, see Table 1) it is formulated in terms of the specific combination of components used in each study. The transitivity assumption now states that we can use studies comparing the X vs. the Y combination of components (XY studies) and also XZ studies to learn about the relative effects of group of components Y vs. group of components Z. Under this formulation the X and Y combinations might even be different forms of the same composite intervention (e.g. they might both fall under the general name of CBT, but might have different constituent components).

In order to assess the plausibility of this assumption we will summarize important trial and patient-level characteristics for each pairwise comparison for which direct evidence is available in the network. We will then visually inspect the similarity of factors that are considered to be effect modifiers (duration of the therapy, percentages of agoraphobic, depressed and drug-treated patients). We will also investigate the inclusion and exclusion criteria of all trials in the network to make sure that patients, treatments and outcomes in the trials are sufficiently similar in all aspects that modify the treatment effect.

To evaluate inconsistency in the entire network we will employ the design-by-treatment interaction model ([Higgins 2012](#)). This model adds an inconsistency factor to each closed formed in the network and then estimates a Q statistic that tests the consistency assumption in the network. Our primary analysis assumes consistency for the relative components effects. Consequently, we will estimate the inconsistency model for the detailed network where each combination of components will define a different network node. We expect this network to be very scarce (with many nodes and few data per comparison) and therefore underpowered to detect important inconsistencies. To improve power we will estimate the design-by-treatment interaction model for the 'grouped' network where each treatment (as in table 1) defines a different node. Note that inference from this network would infer about inconsistency for the relative treatment effects and not for the relative component effects. For both networks, we will report the Q statistic, its p-value and the overall  $I^2$  for inconsistency in the network ([Jackson 2014](#)).

### ***Assessment of the additive treatment effects assumption***

The component-level NMA model we described assumes that the effect of each composite treatment is the sum of the effects of its components. To evaluate this assumption we will first compare the results from studies that compare two specific components  $c_1$  vs  $c_2$  to the results from studies that compare these the same two components but also involve a third one  $c = \{w, pl, pe, ps, br, mr, ct, ine, ive, vre, 3w, ftf\}$  in both arms. That is studies comparing  $c_1$  vs  $c_2$  should provide similar ORs with studies that compare  $c_1 + c$  vs  $c_2 + c$ . Large heterogeneity between the various designs that compare  $c_1$  vs  $c_2$  with and without an add-on treatment could indicate that the additivity assumption might not hold. Then we will examine multi-arm studies that compare components and combinations thereof (for example three arm studies that compare  $c_1$  vs  $c_2$  vs  $c_1 + c_2$ ) for

support of the additivity assumption. If data permit we will explore other models with respect to the synergistic or antagonistic association between components as discussed by Welton et al. ([Welton 2009](#)).

### ***Accounting for small-study effects and reporting biases***

One important finding in our previous Cochrane review ([Pompoli 2015](#)) is that small-study effects (SSE) are very likely to operate in this field, i.e. smaller studies tended to report larger effect sizes. More specifically, we found that small studies provide systematically larger effects for the CBT vs. WL comparison for short-term remission and short-term response. This effect might be due to publication bias (which means that smaller studies not showing statistically significant results were not published) or due to important methodological differences between smaller and bigger studies. We did not find any evidence of SSE for the head-to-head comparison between active treatments nor in the short-term tolerability outcome.

In order to account for the existence of SSE and to provide adjusted relative effect estimates we will use the methodology described in ([Chaimani 2012](#), [Mavridis 2015](#)), i.e. we will perform a meta-regression on the variance of the effect estimate in each study comparing active intervention vs. an intervention with the waiting component (w), assuming a common coefficient across all comparisons.

### ***Subgroup analysis and investigation of heterogeneity***

In our previous analyses ([Pompoli 2015](#)) we did not detect any association between the relative treatment effects and variables such as year of publication, percentage of drug-treated patients, percentage of patients with comorbid depression and percentage of agoraphobic patients. This might have been due to low power and we do not expect that power will be considerably improved in this updated component-level network. Therefore we don't plan any subgroup analysis

### ***Sensitivity analysis***

If data permits, we are planning to run a sensitivity analysis by restricting our database to include only studies considered to be at low risk of selection and detection bias (i.e. adequate allocation sequence generation, adequate allocation concealment, blinding of assessor).

### **Contribution of authors**

TAF conceived the idea. AP drafted the protocol. TAF, GS and OE provided methodological and statistical advice. HI, AT, HN provided suggestions and input. All authors reviewed and approved the final version of the protocol.

### **Competing interests**

None.

## **Funding**

This work was supported in part by the Japan Society for the Promotion of Science KAKENHI Grant-in-Aid for Challenging Exploratory Research (grant n°26670314), the European Research Council (ERC Starting Grant IMMA 260559) and the Innovative Medicines Initiative Joint Undertaking under grant agreement no 115546.

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## **Appendices**

### **Appendix 1: CCDANCTR-References Register Search**

1. (therap\* or psychotherap\*) [ti,ab]
2. psychotherapy [kw]
3. (acceptance\* or commitment\* or “activity scheduling” or adlerian or art or aversion or brief or “client cent\*” or cognitive\* or color or colour or compassion-focused or “compassion\* focus\*” or compassionate or conjoint or conversion or conversational or couples or dance or dialectic\* or diffusion or distraction or eclectic or (emotion and focus\*) or emotion-focus\* or existential or experiential or exposure or expressive or family or focus-oriented or “focus oriented” or freudian or gestalt or “group” or humanistic or implosive or insight or integrative or interpersonal or jungian or kleinian or logo or marital or metacognitive or meta-cognitive or milieu or morita or multimodal or multi-modal or music or narrative or nondirective or non-directive or “non directive” or nonspecific or non-specific or “non specific” or “object relations” or “personal construct” or “person cent\*” or person-cent\* or persuasion or play or ((pleasant or pleasing) and event\*) or primal or problem-focused or “problem focused” or problem-solving or “problem solving” or process- experiential or “process experiential” or psychodynamic or “rational emotive” or reality or “reciprocal inhibition” or relationship\* or reminiscence or restructuring or rogerian or schema\* or self-control\* or “self control\*” or “short term” or short-term or sex or “social effectiveness” or “social skill\*” or socio-environment\* or “socio environment\*” or “solution focused” or solution-focused or “stress management” or supportive or time-limited or “time limited” or “third wave” or transference or transtheoretical or validation)
4. (abreaction or “acting out” or “age regression” or ((assertive\* or attention or autogenic or mind or sensitivity) and train\*) or autosuggestion or “balint group” or ((behavior\* or behaviour\*) and (activation or therap\* or treatment or contracting or modification)) or bibliotherap\* or biofeedback or catharsis or \*cognitive\* or \*CBT\* or “mind training” or counsel\* or “contingency management” or countertransference or “covert sensitization” or “eye movement desensiti\*” or EMDR or “crisis intervention” or “dream analysis” or “emotional freedom” or “free association” or “functional analys\*” or griefwork or hypno\* or imagery or meditation\* or “mental healing” or

mindfulness\* or "panic program" or psychoanaly\* or psychodrama or psychoeducat\* or (psycho\* and support\*) or psychotherap\* or relaxation or "role play\*" or "self analysis" or "self esteem" or "self-help or "self help" or "sensitivity training" or "support group\*" or therapist or "therapeutic technique\*" or "transactional analysis")

5. ((1 or 2) and 3) or 4

6. panic

7. (5 and 6)

## **Appendix 2: PubMed search strategy**

((("randomized controlled trial"[Publication Type]) OR ("controlled clinical trial"[Publication Type]) OR ("clinical trials as topic"[MeSH Terms]) OR ((randomized[Title/Abstract]) OR randomised[Title/Abstract]) OR (randomly[Title/Abstract]) OR (placebo[Title/Abstract]) OR (trial[Title]))) NOT ("animals"[MeSH Terms] NOT "humans"[MeSH Terms])) AND (("psychother- apy"[MeSH Terms]) OR (psychotherap\* OR psychoanaly\* OR psychodynamic OR psychodrama OR psychoeducat\*[Title/Abstract])) AND (("agoraphobia"[MeSH Terms]) OR ("panic disorder"[MeSH Terms]) OR ("panic"[MeSH]) OR (panic OR agoraphobi\*[Title/ Abstract]))