Psychological therapies for panic disorder with or without agoraphobia in adults

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Background

Description of the condition

A panic attack is a discrete period of fear or anxiety that has a rapid onset, reaches a peak within 10 minutes and in which at least four of thirteen characteristic symptoms are experienced. Many of these symptoms involve bodily systems, such as racing heart, chest pain, sweating, shaking, dizziness, flushing, stomach churning, faintness and breathlessness. Further recognised panic attack symptoms involve fearful cognitions, such as the fear of collapse, going mad or dying, and derealization (APA 2000).

According to the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV-TR, APA 2000), panic disorder is characterized by the presence of recurrent unexpected panic attacks, of which at least one has been followed by one month (or more) of persistent concern about having additional attacks, worry about the implications of the attack (or its consequences) or a significant change in behavior related to the attacks.

Panic disorder is common in the general population, with a lifetime prevalence of 1% to 4% (Eaton 1994; Bijl 1998). In primary care settings panic syndromes have been reported to have a prevalence of around 10% (King 2008). Its aetiology is not fully understood and is probably heterogeneous. Biological theories incorporate the faulty triggering of an inbuilt anxiety response, possibly a suffocation alarm. Evidence for this comes from biological challenge tests (lactate and carbon dioxide trigger panic in those with the disorder) and from neuroimaging studies that show activation of fear circuits, such as that involving the periaqueductal grey matter (Gorman 2000).

Agoraphobia is anxiety about being in places or situations from which escape might be difficult or embarrassing or in which help may not be available in the event of having a panic attack (APA 2000). Agoraphobia can occur with panic disorder: in the general population, about one quarter of people suffering from panic disorder also have agoraphobia but this proportion is much higher in the clinical samples (Kessler 2006). The presence of agoraphobia is associated with increased severity and worse outcome (Kessler 2006). There are several risk factors that predict the development of agoraphobia in people suffering from panic disorder: female gender, more severe dizziness during panic attacks, cognitive factors, dependent personality traits and social anxiety disorder (Starcevic 2009).

Panic disorder, with or without agoraphobia, is highly comorbid with other psychiatric disorders such as drug dependence, major depression, bipolar I disorder, social phobia, specific phobia, generalized anxiety disorder (Grant 2006). It is estimated that generalized anxiety disorder co-occurs in 68% of people with panic disorder, whilst major depression has a prevalence of 24% to 88% among people with panic disorder (Starcevic 2009).

Description of the intervention

Recent guidelines from the National Institute for Health and Clinical Excellence (NICE 2011) recommend three types of intervention in the care of individuals with panic disorder, any of which should be offered promptly and taking into account the preference of the patient. According to the NICE guidelines, the interventions that have evidence for the longest duration of effect, in descending order, are psychological therapy, pharmacological therapy (antidepressant medication) and self-help.

A psychological therapy can be defined as a therapeutic interaction between a trained professional and a patient (or a group of patients), by way of their verbal and non-verbal communication, for the purpose of ameliorating the sufferings on the part of the patient(s).

Although NICE guidelines recommend the use of cognitive behavioural therapy (CBT) for the treatment of panic disorder, many other psychological therapies have been proposed as viable therapeutic options. Each therapy is characterized by a certain theoretical framework, according to which a set of therapeutic ingredients (or "components") and technical features are defined.

A further level of distinction among psychological therapies concerns the form of delivery of the intervention. To this regard, NICE guidelines suggest that the intervention (CBT) should be optimally delivered in the form of one to two hours' weekly sessions, for a total of seven to 14 hours within a maximum of four months since commencement. However, different variables have been, and still remain, subject of investigation of cost-effectiveness analyses. Among these variables, the number of sessions, the duration of treatment and the therapeutic setting (group versus individual; face-to-face versus remote versus self-help) have been explored.

How the intervention might work

The main features and rationale of the psychological therapies considered for this review can be summarised as follows:

Psychoeducation consists of providing patients with information about their psychological disease. In this context, it can be explained to patients that their symptoms can be interpreted in the light of a certain cause-effect model, according to a more general theoretical framework that can vary across the different psychological approaches. The rationale of psychoeducation is that providing anxious patients with a better understanding of their sufferings may itself lead to a symptom relief (Clark 1985, Sorby 1991). This may be especially important in panic disorder, where the cognitive coping mechanisms of the patients are disrupted and where anticipatory anxiety may cause additional attacks (Dannon 2002). In this sense, as the authors further suggest, a psychoeducational intervention may increase the patients' sense of control, leading to a reduction of catastrophic thoughts and emotions.

Psychological support can be intended as any emotional support that arises through the interaction between a patient and a professional therapist. In this broad sense, it may be regarded as a common component of any other psychological therapy. However, even on its own, psychological support may itself represent a psychological therapy (i.e. supportive psychotherapy). According to the manual of Winston, Rosenthal and Pinsker (Winston 2004), supportive psychotherapy is a dyadic treatment that uses direct measures to ameliorate symptoms and maintain, restore, or improve self-esteem, ego function, and adaptive skills.

Although different techniques can be used (e.g. encouragement, rationalizing and reframing, anticipatory guidance, etc.) therapeutic alliance represents the most important element of the therapy (Winston 2004). Rogerian client-centred psychotherapy (Rogers 1980) is probably the most representative example of supportive psychotherapy. In this approach, within the context of a warm, empathic and non-directive therapeutic relationship, clients are lead to become aware of their true feelings and to fully accept themselves as they are, including imperfections and dysfunctions. Non-specific in nature, supportive psychotherapy is not designed for the treatment of a psychiatric disorder in particular. In this sense, the supportive treatment of panic disorder and/or agoraphobia does not differ from the treatment of any other disorder. Although scarce, the available body of evidence does not exclude a possible role of psychological support in the treatment of agoraphobia (Zitrin 1978, Klein 1983); its efficacy in the treatment of panic disorder without agoraphobia still remains unclear.

Physiological therapies are represented by a set of different possible treatments that use some kind of physical training (e.g. breathing retraining, relaxation techniques, biofeedback) in order to help the patient to control the physiological manifestations of anxiety. Among the physiological therapies proposed for the treatment of panic disorder, breathing retraining and relaxation techniques are probably the most studied. Respiratory abnormalities, with particular regard to hyperventilation and hypocapnia, have been postulated as being important factors in the development or maintenance of panic disorder (Ley 1985, Klein 1993, for a review, see Meuret 2010b). According to the model proposed by Ley 1985, panic attacks are caused by acute states of hypocapnia, in a positive feedback loop between hyperventilation and anxiety. Therefore, amelioration of panic symptoms is expected when patients achieve reductions in transient and sustained hypocapnia. To reach this goal, different strategies have been proposed, although most manuals and studies describe instructions in abdominal breathing as their central technique (Meuret 2012). Results on the efficacy of breathing training in the treatment of panic disorder are mixed (Meuret 2010b).

Progressive muscle relaxation (PMR), as formalized by Bernstein and Borkovec (Bernstein 1973), can be taught to panic patients in order to reduce general tension and achieve a body state that lowers the risk for stressors to elicit panic. The so-called applied relaxation (Ost 1987) is a slightly different form of physiological therapy, in which relaxation training and exposure are combined. The purpose of applied relaxation is to teach the patient to observe the very first signs of a panic attack and to apply a rapid and effective relaxation technique to cope with, and eventually abort these symptoms before they develop into a panic attack. With regard to remission from panic disorder, in a direct comparison applied relaxation wasn't found to be significantly better than PMR at the end of treatment, although it performed better than PMR on six out of 11 measures (Ost 1988).

Cognitive therapy finds its roots in the work of Albert Ellis and Aaron Beck. Its main component is represented by cognitive restructuring, a psychotherapeutic process of learning to identify and dispute irrational or maladaptive thoughts using strategies such as Socratic questioning, thought recording and guided imagery. In the case of panic disorder, it has been proposed that panic attacks result from the catastrophic misinterpretation of certain bodily sensations (Clark 1986a). The catastrophic misinterpretation involves the sufferer perceiving sensations involved in normal anxiety responses as much more dangerous than they really are, for example perceiving palpitations as evidence of impending heart attack. The cognitive approach would involve identifying patients' negative interpretations of the bodily sensations experienced in panic attacks, suggesting alternative non-catastrophic interpretations of the sensations and then helping the patient to test the validity of these alternative interpretations. As pointed out in a recent review (Meuret 2012), CT is often intermingled with behavioral techniques (e.g., "behavioral experiments," "hypothesis testing," "instructions" involving exposure), which complicates the testing of efficacy of CT in its "pure" form. Nonetheless, there is some evidence that training in cognitive procedures in full isolation from exposure and behavioral procedures is efficacious in reducing aspects of panic (Beck 1994, Meuret 2010a, Salkovskis 1991, Van den Hout 1994).

Behaviour therapy is characterized by the use of some kind of exposure in order to modify dysfunctional behaviours that may contribute to the development and persistence of psychological symptoms. The principle of exposure in the treatment of phobic disorders is to persuade the patient to enter and stay in his/her phobic situation until he/she feels better, and to do this repeatedly until it becomes so customary that it holds no more terror (Marks 1981). In the specific case of panic disorder, the behavioural therapy consists of graded exposure to the body sensations which accompany panic ("interoceptive exposure") and/or to situations perceived as threatening ("in vivo exposure", "imagery exposure", "virtual reality exposure") in order to progressively reduce the patient's apprehensive reaction towards them. There is evidence that exposure strategies alone are effective in the treatment of panic disorder (Williams 1996, Ost 2004, Gloster 2011).

The above description of cognitive and behavioral therapies shows that these two approaches may well be regarded more as complementary than alternative. Cognitive-behavioral therapy combines elements of both in order to reduce emotional distress and psychological symptoms, assuming that cognitions, behaviours and emotions are interrelated. Cognitive-behavioral therapy for panic disorder is usually administered according to the manuals of Clark 1986b and Barlow 2000. Its main components are represented by psychoeducation, breathing retraining, progressive muscle relaxation, cognitive restructuring, behavioral experiments, interoceptive exposure and in vivo exposure. A fairly consistent body of evidence exists in support of the efficacy of cognitive-behavioral treatment, administered either in individual or group sessions, for panic disorder (among others: Telch 1993,Clark 1999, Dow 2000, Hendriks 2010). Furthermore, a growing body of evidence supports the efficacy of self-administered versions (e.g. book-based, internet-based) of this psychological therapy (Carlbring 2006, Nordin 2010, Wims 2010).

The so-called "third wave" therapies are represented by a set of different therapies (e.g. mindfulness, acceptance and commitment therapy), all originating from the cognitive-behavioural approach, compared to which more importance is given to the form, rather than the content, of patients' thoughts. By focusing on the function of cognition these approaches aim to help patients to develop more adaptive emotional responses to situations. When mindfulness and acceptance are applied to anxiety disorders, the aim is for the individual to be able to observe symptomatic processes without overly identifying with them or without reacting to them in ways that further distress (Roemer 2008). A systematic review and meta-analysis of mindfulness-

and acceptance-based interventions for anxiety disorders has been recently published (Vollestad 2012). As summarized in Ludwig 2008, mindfulness involves attending to relevant aspects of experience in a nonjudgmental manner. The goal of mindfulness is to maintain awareness moment by moment, disengaging oneself from strong attachment to beliefs, thoughts, or emotions, thereby developing a greater sense of emotional balance and well-being. An aim of mindfulness practice is to take greater responsibility for one's life choices. Although scarce, some evidence exists in support of the efficacy of this therapy for the treatment of generalized anxiety disorder and panic disorder (Lee 2007, Kim 2009). As originally developed (Hayes 1999), ACT was intended for the treatment of psychopathology in general rather than a specific disorder in particular. ACT conceptualises psychological events as a set of ongoing interactions between whole organisms and historically and situationally defined contexts. Removal of a client's problematic behaviours from the contexts that participate in that event (e.g., merely analysing manifested behavioral symptoms themselves) is thought to miss the nature of the problem and avenues for its solution. ACT clients are therefore encouraged to embrace a passionate and ongoing interest in how to live according to their values. In ACT there is a conscious posture of openness and acceptance toward all psychological events, even if they are formally "negative" "irrational" or even "psychotic". For example, if the client feels trapped, frustrated, confused, afraid, angry, or anxious, the ACT stance suggests this is not so much a problem as it is an opportunity to work on how powerful events in the here and now can become barriers to growth (Hayes 2004). Some evidence supports that ACT may be as effective as CBT in the treatment of anxiety disorders, including panic disorder (Arch 2012).

Psychodynamic therapies consist of a set of psychological therapies, different in length and depth, represented by psychoanalysis (as conceptualised by S. Freud) and its further developments. According to these approaches, psychological symptoms can be seen as manifestation of intrapsychic or unconscious conflicts: these therapies use different therapeutic strategies (e.g. unconscious contents exploration, dream analysis, analysis of past experiences, analysis of parental relationships, analysis of transference, analysis of resistances) in order to reveal and resolve such conflicts. In the specific case of panic disorder, Busch and colleagues (Busch 1996) proposed that during childhood, a sense of fearful dependency on the parent may lead to the development of anger towards him/her. As a consequence, a vicious cycle develops in which the child's anger threatens the needed tie to the parent and thereby increases fearful dependency, which promotes further frustration and rage at the parent. This cycle may then recur in adulthood, when threats to attachment trigger intense feelings of abandonment, anger, and anxiety, leading to the development of the disorder. The aim of psychodynamic psychotherapy is to address such underlying psychological factors in order to obtain an improvement of panic symptoms. Although only a few studies have explored the effects of psychodynamic psychotherapy for panic disorder, the available evidence suggests the viability of this approach as a valid therapeutic option (Wiborg 1996, Milrod 2007).

Why it is important to do this review

A previous Cochrane meta-analysis comparing combined psychotherapy plus antidepressants versus psychotherapy alone or pharmacotherapy alone (Furukawa 2007) showed the superiority of combined therapy over either monotherapies in the short term, and that of combined therapy and psychotherapy alone over pharmacotherapy alone in the long term, thus suggesting that either combined therapy or psychotherapy alone can be chosen as first line treatment for panic disorder with or without agoraphobia. In particular, behavioural and cognitive-behavioural psychotherapies showed the strongest evidence. Another meta-analysis, aimed at analysing the efficacy of psychological interventions versus control conditions in the treatment of panic disorder with or without agoraphobia (Sánchez-Meca 2010), showed a general efficacy of psychological therapies over different clusters of symptoms, with the most consistent results in favour of the combination of exposure strategies with relaxation training and/or breathing retraining techniques. The study conducted by Sánchez-Meca et al. revealed the presence of substantial heterogeneity among included studies (I^2 = 70.4%). The authors examined the observed heterogeneity with exploratory (i.e. uncorrected for multiple testing) secondary analyses, suggesting the role of different factors in accounting for the observed variance. Among these, the following seem to be particularly noteworthy: type of therapy, type of control group and percentage of patients with agoraphobia. The observed degree of heterogeneity due to differences in the psychological therapies suggests that some psychotherapies may be more effective than others in the treatment of the disorder. However, both the existence and the eventual magnitude of such differences remain unclear. This is partly due to the presence of methodological diversity among available studies: as suggested by Sánchez-Meca et al., the type of control group may significantly influence the measured effect size, limiting the possibility of drawing conclusions. A further consideration is that only a few trials compared different psychological approaches with each other and, more generally, psychological therapies have not been all equally investigated.

In the attempt to overcome these issues, in this review we will perform a network meta-analysis (NMA), also known as multiple treatment meta-analysis, in which 9 different forms of psychological intervention and 3 forms of control condition (see Types of interventions) will be independently compared with each other. We expect this methodological strategy to reduce the amount of heterogeneity observed in previous studies. Furthermore, by synthesizing the available direct and indirect evidence via NMA, it will be possible to obtain an overall effect-size estimate for each possible pair of therapies in the network, even for interventions which have not been directly compared with each other in previous trials. This will allow us to disclose and assess differences in effects not only among experimental interventions, but also among control conditions. Finally, it will be possible to calculate a probabilistic ranking in order to help the identification of those interventions which are more likely to be more effective than others in the treatment of panic disorder.

Objectives

To assess the comparative efficacy and acceptability of different psychological therapies and different control conditions for panic disorder with or without agoraphobia in adults.

Methods

Criteria for considering studies for this review

Types of studies

All randomised controlled trials (RCTs), comparing one type of psychotherapy against another or against a non-pharmacological control condition in the short and long term treatment of panic disorder.
Cluster-randomized trials will be included when effects of clustering are taken account of.
Crossover randomised trials will be included, but only results from the first randomization period will be considered.
Studies in which the replacement of dropouts is allowed will be included as long as replacements are low in number (less than 15% of the final sample) and evenly distributed among treatment arms.
Quasi-randomized controlled trials (in which treatment assignment was decided through methods such as alternate days of the week) will be excluded.

Types of participants

Age range

Patients, aged 18 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 or above.

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) or ICD-10 (WHO 1992).
There is evidence that over 95% of patients with agoraphobia seen clinically suffer from panic disorder as well (Goisman 1995). According to this finding, studies focusing on agoraphobia, rather than panic disorder, will be included 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. The effect of the inclusion of trials with different percentages of patients suffering from agoraphobia will be explored in a meta-regression analysis.

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.

Co-morbidities

We will include studies where participants have other anxiety disorders (e.g. generalised anxiety disorder, specific phobias) or with subthreshold panic disorder if: 1) separate results for patients with panic disorder are reported and 2) randomizations is stratified by specific diagnoses. Stratification by diagnosis will not be required if the total sample includes at least 40 participants with panic disorder.
We will exclude studiesin which all participants had a concurrent primary diagnosis of Axis I or II disorders other than panic disorder or agoraphobia.
We will include studies in which the participants have physical comorbidities.
However, we will exclude studies which explicitly focus on panic disorder or agoraphobia among patients with a certain physical comorbidity.

Types of interventions

Experimental interventions

The following psychological treatments will be included:

1. PE - Psychoeducation, intended as sessions in which patients are only provided informations about their disease.
2. SP - Supportive Psychotherapy, with or without a psychoeducational component, intended as sessions in which patients are administered an active, although non-specific, psychological treatment.
3. PT - Physiological therapies that use some kind of physical training (e.g. breathing retraining, progressive muscle relaxation, applied relaxation) in order to reduce the physiological manifestations of anxiety.
4. BT - Behaviour therapy, with or without physiological components, aiming at patient's habituation to anxiety provoking situations and/or sensations through some kind of exposure (e.g. interoceptive, in vivo).
5. CT - Cognitive therapy, with or without physiological components and behavioral experiments, aiming at the modification of maladaptive thoughts through some kind of cognitive restructuring.
6. CBT - Face-to-face cognitive-behaviour therapy, with or without physiological components, containing both cognitive and behavioural therapy elements.
7. SH CBT - Non face-to-face cognitive-behaviour therapy, described as above, in its book/computer/internet version, administered with or without minimal therapist contact.

8. 3W - Third Wave CBT, including Acceptance and commitment therapy, mindfulness-based therapy and other so-called "third wave" therapies, administered with or without other CBT components (e.g. exposure, cognitive restructuring, breathing retraining, muscle relaxation).
9. PD - Psychodynamic therapies focused on revealing and resolving intrapsychic or unconscious conflicts.

Therapies can be of any length so that those given in a single session will be accepted.
We will exclude combination therapies, other than those listed below. However, studies in which a pharmacological co-administration is allowed will be included as long as there are no systematic differences in drug administration between the study arms. The percentage of studies in which a drug co-administration is allowed, the percentage of studies that require a stabilization of therapy and, in this latter case, the time of required stabilization, will be reported.
Both individual and group therapies will be included.
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.
So-called component studies (e.g. dismantling studies) will be included as long as each arm can be regarded as any of the above-defined experimental interventions compared against another experimental or comparator treatment. Eventually, study arms may be regarded as giving information about the same experimental intervention and thus be combined.
We will exclude interpersonal psychotherapy, emotion-focused therapy and any other approach not specifically designed for the treatment of panic disorder, such as Morita therapy, Eye Movement and Desensitization Reprocessing (EMDR), Music therapy and simple physical exercise..
With the exception of Self Help CBT, therapies must be administered face-to-face.
We will exclude therapies remotely administered (e.g. through phone calls or video calls).
In the case of Psychoeducation, the simple provision of informational material without any face-to-face session will not be considered an active intervention.
When psychoeducation and/or psychological support are accompanied by any other psychological intervention, study arms will be classified accordingly to the latter and psychoeducation and psychological support will be regarded as components of that intervention.

Comparator interventions

1. NT - No psychological treatment (participants receive assessment only, with or without simple provision of informational material and/or minimal therapist contact, and they know that they will not receive the active treatment in question after the trial).
2. WL - Waiting List (participants receive assessment, with or without simple provision of informational material and/or minimal therapist contact, and they know that they will receive the active treatment in question after the waiting phase).
3. APP - Attention or psychological placebo (participants receive a face-to-face inactive* intervention that can be perceived both as ineffective or, respectively, effective).

Given the general inconsistency of the definitions of comparator interventions among different studies, the attribution of a control group to one of these prespecified categories will rely on its detailed description rather than on the name given by the authors. However, where a sufficiently detailed descriptionis unavailable, either from the paper or by contacting the original authors, the attribution will solely rely on the given definition. Particular inconsistency exists in the definition of what is intended for treatment as usual (TAU). When TAU is intended as no treatment, waiting list or psychological support, groups will be classified accordingly.
*Attention placebo is defined as any form of inactive intervention designed by the original authors to be perceived as ineffective by patients; psychological placebo is defined as any form of inactive intervention designed by the original authors to be perceived as effective by patients. The inclusion of an intervention among attention or psychological placebo groups requires that intervention to be inactive. Any form of active intervention will therefore be included among experimental interventions even if defined as a control condition by the original authors.
We will exclude studies in which a pharmacological placebo is either co-administered or used as control condition.
In total we expect the network to have 12 nodes each one representing an intervention or control (see Data synthesis).

Types of outcome measures

Primary outcomes

1. Short term[a] remission[b] of panic disorder with or without agoraphobia.
2. Short term response[c] of panic disorder with or without agoraphobia.
3. Dropouts for any reason in the short term

([a]) Short term, i.e. within six months from treatment commencement. When multiple time-point measures are available, preference will be given to measures at approximately three months after treatment commencement.
([b]) "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 (Guy 1976).

([c]) "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 Change Scale (Guy 1976), more than 40% reduction in the score of Panic Disorder Severity Scale (Shear 1997), and more than 50% reduction in the Fear Questionnaire Agoraphobia Subscale (Marks 1979). When more than one index of remission/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 same criteria used for the continuous scale outcome (see below).

Secondary outcomes

1. Short term improvement of panic disorder with or without agoraphobia as measured on a continuous scale[d].
2. Long term[e] remission/response[f] of panic disorder with or without agoraphobia.

([d]) Examples would be Panic Disorder Severity Scale (total score 0 to 28), Panic and Agoraphobia Scale (total score 0 to 45), Clinical Global Impression Severity Scale (1 to 7), Clinical Global Impression Change Scale (1 to 7), etc. When more than one scale is available in the paper, preference will be given in the following order:

- PDSS > PAS > ASI-R > ASI> ACQ > BSQ > other scales specific for panic disorder
- CGI-S > CGI-I > GAS > GAF > other global scales
- FQ-ag > FQ-global > MI-AAL > MI-AAC > other scales specific for agoraphobia only
- Panic frequency > panic severity > other scales specific for panic attacks only

Once the scale has been chosen, if both self and observer-rated assessments are available, preference will be given to the latter. The actual measure entered into meta-analysis is indicated at the top of the listings in the Table of Included Studies.

([e]) Long term, i.e. six months or longer after treatment commencement, either on treatment discontinuation or on continued treatment (in the case of long-term therapies). When multiple time-point measures are available, preference will be given to measures at approximately 12-15 months after treatment commencement. In the case of missing data at the long term assessment, studies will be considered for the analyses as long as dropouts are low in number (< 30% of the original sample) and evenly distributed across treatment arms.

([f]) "Response" and "Remission" are intended as above. It is likely that not all studies will report both response and remission rates in the long term. When both remission and response rates are reported, we will consider the former. However, if remission rates are not reported but response rates are available, these will be used for the analyses.

Search methods for identification of studies

CCDAN's Specialized Register (CCDANCTR)

The Cochrane Depression, Anxiety and Neurosis Group (CCDAN) maintain two clinical trials registers at their editorial base in Bristol, UK, a references register and a studies based register. The CCDANCTR-References Register contains over 31,500 reports of trials in depression, anxiety and neurosis. Approximately 65% of these references have been tagged to individual, coded trials. The coded trials are held in the CCDANCTR-Studies Register and records are linked between the two registers through the use of unique Study ID tags. Coding of trials is based on the EU-Psi coding manual. Please contact the CCDAN Trials Search Coordinator for further details. Reports of trials for inclusion in the Group's registers are collated from routine (weekly), generic 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 are also sourced from international trials registers c/o the World Health Organisation’s trials portal (ICTRP), drug companies, the hand-searching of key journals, conference proceedings and other (non-Cochrane) systematic reviews and meta-analyses.

Details of CCDAN's generic search strategies can be found on the Group‘s website.

Electronic searches

The CCDANCTR-Studies Register will be searched using the following terms:

Condition/Comorbidity = panic
AND
Intervention = (attention* or behav* or biblio* or biofeedback or cognitive or collaborative or contact or counsel* or desensiti* or educat* or expos* or feedback or ”group” or imag* or interpersonal or intervention or management or panic or prevention or psycho* or relaxation or self* or stress* or support* or *therap* or *train* or treatment or unclear or ”not stated”)

The CCDANCTR-References Register will be searched using a more sensitive set of terms to identify additional untagged/uncoded reports of RCTs (Appendix 1)

A further search of the CCDANCTR will be conducted to identify reports of studies for ‘Anxiety Disorders Not Otherwise Specified’ (ADNOS).

The CCDANCTR-Studies Register will be searched for CONDITION = "Anxiety Disorder*"

Pharma studies and studies in children/adolescents will be manually screened out.

The CCDANCTR-References Register will be searched using the following terms to identify additional untagged/uncoded reports of RCTs for ADNOS:

("anxiety disorder*" and not (agoraphobi* or panic or (social and (anxi* or phobi*)) or generalised or generalized or obsessive or compulsive or OCD or PTSD or post-trauma* or "post trauma*" or posttrauma*)) + (terms for psychotherapies as listed in Appendix 1).
Pharma studies and studies in children/adolescents retrieved from this sensitive search of the references register will be manually screened out.

Supplementary searches

Complementary searches will be conducted on PubMed (Appendix 2) as well as on trials registries such as the WHO International Clinical Trials Registry Platform (http://apps.who.int/trialsearch/) and Clinicaltrials (http://clinicaltrials.gov/).
There will be no restrictions on date, language or publication status applied to the searches.

Searching other resources

Reference lists

The reference lists of all included studies and relevant systematic reviews will be checked to identify additional studies missed from the original electronic searches.

Citation indexes

A citation search will be conducted on the Web of Science to identify articles citing any of the included studies.

Personal communication

Trialists and subject experts will be contacted for information on unpublished or ongoing studies or to request additional trial data.

Grey literature

The database OpenSIGLE (http://www.opengrey.eu/) will be searched to identify reports of trials not formally published in books or journals.

Data collection and analysis

Selection of studies

At least two out of three review authors (AP, AT, HI) will examine 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). Agreement between review authors in the study selection will be reported. The discordance in the selection of studies will be evaluated quantifying both the percentage of agreement and Cohen's Kappa (k) (Cohen 1960). Where it is not 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 exclusions 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, pilot-tested, Excel data collection form to independently extract the data from included studies. Extracted data will concern: study design, administered interventions (format and timing of psychotherapy and control condition, therapist training, intervention components), participants' characteristics (diagnostic criteria, percentage of agoraphobic patients), outcomes, risk of bias and publication. Again, any disagreement will be resolved either by discussion or by consultation of a fourth member of the review team (TAF). If necessary, authors of studies will be contacted to obtain further clarification. Agreement between data extractors will be reported.

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 in included studies using the tool described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). The following domains will be assessed:

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 reporting (Attrition bias)
5. Selective outcome reporting (Reporting bias)

The risk of bias, in each domain and overall, will be assessed and categorized into:

- Low risk of bias, plausible bias unlikely to seriously alter the results
- High risk of bias, plausible bias that seriously weakens confidence in the results
- Unclear risk of bias, plausible bias that raises some doubt about the results

Where inadequate details of randomization and other characteristics of trials are provided the risk of bias will be classified as unclear, unless further information can be obtained by contacting the authors. If the assessors disagree, the final rating will be made by discussion or with the involvement of another member of the review group (TAF) if necessary. Agreement between the two independent raters in the risk of bias assessment will be reported.

Therapist and researcher allegiance, as well as treatment fidelity, will be assessed as possible sources of performance bias. Blinding of therapists, the common way to minimize the risk of performance bias, is not feasible in these kinds of study.
The risk of detection bias will be evaluated for the first of the primary outcomes only. Studies will be classified as having a low risk of detection bias when the identification of a patient as a "remitter" requires at least one observer rating and the observer is blind to the treatment allocation.
Risk of attrition bias will be calculated separately for short-term and long-term outcomes. A study will be classified as being at low risk of attrition bias when data for all randomised patients are available at short/long term assessment. In the case of dropouts, a study may still be assessed as being at low risk of attrition bias when:

- Missing outcome data are few and balanced in numbers across intervention groups, with similar reasons for missing data across groups;
- Reasons for missing outcome data unlikely to be related to true outcome
- Missing data have been imputed using appropriate methods (LOCF will not be considered an appropriate method in itself. It will be considered appropriate only when the LOCF cases are few and balanced between arms).

Whenever possible, study protocols will be retrieved in order to assess the risk of reporting bias. A study will be considered to be at low risk of reporting bias when the study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way. When the study protocol is not available, the study will be classified as being at unclear risk of reporting bias unless reported information are enough to make a judgment (text of this nature may be uncommon).

Measures of treatment effect

Dichotomous data

As measure of treatment effect for binary outcomes we will use the odds ratio (OR) and its 95% confidence interval (CI).

Continuous data

It is likely that different studies have used different panic rating scales; therefore we will use the standardized mean difference (SMD) and its 95% confidence interval (CI). If all included studies have used the same instrument, we will use the mean differences (MD) and its 95% confidence interval (CI).

Endpoint versus change data

We prefer to use scale endpoint data, which typically cannot have negative values and are easier to interpret from a clinical point of view. However, if endpoint data are unavailable, we will use the change data. We consider this strategy to be less prone to selective outcome reporting.

Unit of analysis issues

Cluster-randomised trials

In cluster randomised trials, groups of individuals rather than individuals are randomised to different interventions (Higgins 2011). Cluster-randomized trials will be included when effects of clustering are taken account of.

Cross-over 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 first cross over will be used.

Studies with multiple treatment groups

Where a study involves more than two treatment arms, especially in the case of dismantling studies, arms will be combined as long as they can be regarded as subtypes of the same psychotherapy under review. When arms cannot be regarded as if in each of them a different subtype of the same intervention is administered, we will compare each arm with the common comparator separately. If such a situation occurs, the common comparator arm will be subdivided for pairwise meta-analyses. For example, the sample size and the number of responders of that arm will be halved for dichotomous outcomes; for continuous outcomes, the mean and SD will remain the same but the number of patients included will be halved. In the NMA, multivariate meta-analysis methods will be used to synthesise the results (Higgins 2011, chapter 16.6.3).

Dealing with missing data

We will try to contact the study authors for all relevant missing data. When the LOCF principle has been applied we will use the outcome data as reported by the authors.

Dichotomous outcomes

The proportion of remission and response will be calculated using an intention-to-treat analysis (ITT) following the principle "once randomised always analysed". To this end, all randomised patients for which outcome data are not available will be assumed to be non-responders. This assumption has been used in two previous NMAs (comparing antidepressants and antimanic drugs) and has been proven to be a sensible assumption (Spineli 2013). The same principle will be applied to short and long term outcomes. When dichotomous outcomes are not reported but the means and standard deviations on a panic disorder scale are reported, we will calculate the number of responding or remitted participants according to a validated imputation method (Furukawa 2005).

Continuous outcomes

An "available cases analysis" will be performed in which outcomes will be analysed on an endpoint basis, including patients with either a final assessment or a last observation carried forward to the final assessment as reported in the original report, because we cannot assume any endpoint score for those patients for whom no post-baseline data are available.

Missing statistics

When only P or standard error (SE) values are reported, we will calculate standard deviations (SDs) (Altman 1996). If none of these values is available and in the absence of supplementary data after requests to the authors, the SDs will be calculated according to a validated imputation method (Furukawa 2006).

Assessment of heterogeneity

Pairwise meta-analyses

For each direct comparison, chi^2 and I^2 statistics will be calculated in order to detect the presence of heterogeneity and, respectively, assess its degree. I^2 provides an estimate of the percentage of variability in effect estimates that is due to heterogeneity rather than chance alone (Higgins 2003). I^2 values will be interpreted according to the Cochrane Handbook (Higgins 2011), section 9.5.2. We will also report Tau^2, the between study variance in random-effects meta-analysis. Visual inspection of the forest plots will also be used in order to investigate the presence and nature of statistical heterogeneity.

Network meta-analysis

An assumption underlying NMA is that effect modifiers are similarly distributed across comparisons in the network. That means that an effect modifier should be similar in AB and BC trials in order to obtain a valid AC estimate. Equivalent formulations of the transitivity assumption are presented in Salanti 2012. In order to verify this assumption, for each comparison we will compile a table of important trial and patient characteristics and visually inspect the similarity of factors we consider likely to modify treatment effect. We will also assess the inclusion/exclusion criteria of every trial in the network, to ensure that patients, trial protocols, etc are similar in those aspects which might modify the treatment effect.

Lack of transitivity can be manifested in the data as disagreement between direct and indirect evidence (Caldwell 2005, Lu 2004, Lumley 2002). This can be evaluated statistically by contrasting the direct and the indirect estimates and calculate a test within each closed loop (Bucher 1997, Salanti 2009). We will report the percentage of inconsistent loops in the network and will examine further the data of loops that appear particularly inconsistent. As this approach does not provide an omnibus test and is associated with multiple testing we will also employ other approaches to infer about the statistical inconsistency. First, we will compare the goodness of fit between models that assume consistency and models that do not (pairwise meta-analyses sharing the same heterogeneity parameter). Subsequently we will perform a design-by-treatment interaction test (Higgins 2012). In case that a small amount of inconsistency is found, we will incorporate this in the estimation by fitting inconsistency models (Higgins 2012, Lu 2004).

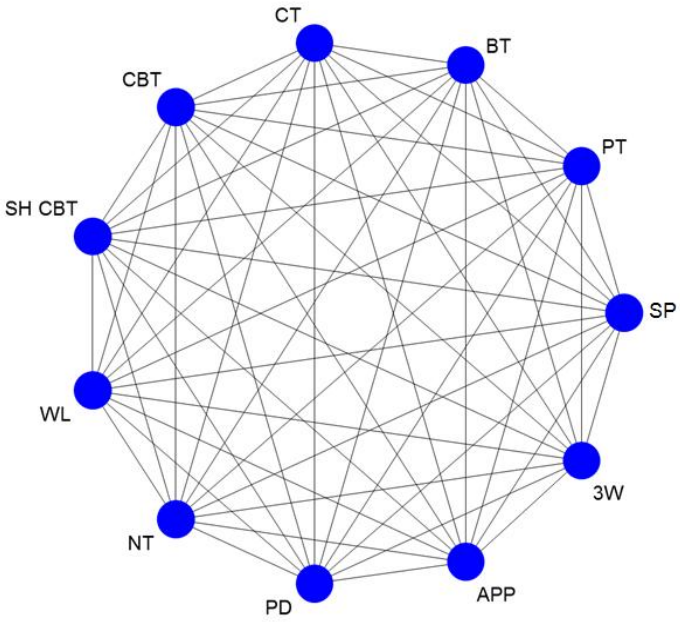
Assessment of reporting biases

We will examine the funnel plots for those pairwise comparisons for which at least 10 studies are available. We will investigate the presence of small study effects for the primary outcomes only: along with visual inspection of the plots, we will formally examine whether the association between estimated intervention effects and the study size is greater than might be expected to occur by chance. We will also apply comparison-adjusted funnel plots for all comparisons in the network as described in (Chaimani 2012).

Data synthesis

Main planned comparisons

The present study is a network meta-analysis and therefore aims to compare all the listed interventions and control conditions against one another in terms of the listed primary and secondary outcomes. In the network, each node will represent an experimental or control condition; comparisons explored in included trials will be represented by lines connecting the nodes. Ideally, the network should consist of 12 nodes, each connected with all the others, meaning that all the listed interventions and each possible comparison among them has been directly explored in at least one included trial (see figure).



Pairwise meta-analyses

For each available comparison explored by at least two trials, we will perform a pair-wise meta-analysis in order to provide overall estimates of treatment effect. Since we expect some clinical heterogeneity between studies, we plan to use a random-effects model to incorporate the assumption that the different studies are estimating different, yet related, treatment effects (Higgins 2011). An “average” treatment effect across the studies will therefore be calculated for each available comparison. For dichotomous outcomes, the

average odds ratio will be calculated with a 95% CI; for continuous outcomes the average SMD (or the MD if all trials use the same scale) will be calculated with a 95% CI.
For this review, the results of pairwise comparisons will be part of the more complex network meta-analyses (see below). However, in order to better show the available "direct" evidence, forest-plots will be presented for pairwise comparisons when at least 10 studies are available.

Network meta-analysis

An indirect comparison allows to estimate the effect of treatment B relative to treatment A via a common comparator C, by statistically combining the summary effects from "A vs C" and "B vs C" studies (Glenny 2005, Caldwell 2005). A NMA combines direct and indirect evidence across a network of studies to make inferences regarding the relative effectiveness of multiple interventions.
A NMA is only possible for a connected set of treatments. A network diagram will be constructed for our primary outcomes in order to evaluate the extent to which treatments are connected.
A random-effects NMA, taking into account the correlations induced by multi-arm trials, will be conducted (Lu 2004, Salanti 2008, White 2012). For each comparison, an average effect estimate along with its 95% credible interval (CrI) will be reported.
Besides yielding relative treatment effects for each comparison, a NMA also allows to estimate the relative ranking of treatments. To rank the treatments according to each outcome accounting for the uncertainty in the treatment effects, we will use the surface under the cumulative ranking curve "SUCRA" (Salanti 2011). The absolute ranks of the treatments per outcome will be presented using "Rankograms" that visually show the distribution of ranking probabilities (Salanti 2011). NMA models typically employ a single heterogeneity parameter. We will report it and we will judge its magnitude against the distribution of values typically found in Cochrane reviews as presented in (Turner 2012).

Subgroup analysis and investigation of heterogeneity

Subgroup and meta-regression analyses are often exploratory in nature and should be interpreted cautiously. Firstly, because these analyses often involve multiple analyses, they may yield false positive results; secondly, these analyses lack power and are more likely to result in false negative results. Keeping in mind the above reservations, we will perform meta-regression analyses to investigate, for the first of the primary outcomes only (Short term remission of panic disorder with or without agoraphobia), the following candidate explanatory variables:

- Year of publication (measured as a continuous variable), as a general proxy for various aspects (e.g. trial quality, definition of diagnosis and outcomes).
- Mean number of treatment sessions: less than 4 sessions, from 4 to 12 sessions, more than 12 sessions. Considerable differences exist in the number of treatment sessions between studies. It seems reasonable to expect this variability to yield some degree of heterogeneity.
- Therapist training: therapist with/without formally recognized specific training in the type of psychotherapy administered.
- Percentage of patients with agoraphobia: measured as a continuous variable. In accordance with Sánchez-Meca 2010, we expect studies including higher percentages of agoraphobic patients to show larger effect sizes.
- Percentage of patients with depression: measured as a continuous variable. We will explore this variable in order to investigate if a psychological intervention specifically designed for panic disorder is less effective in patients with depressive comorbidity.
- Percentage of patients on drug treatment: measured as a continuous variable. Since we are not including studies exploring combined therapies, drug treated patients, when included, are often those who meet the diagnosis of panic disorder despite being on psychopharmacologic treatment. If we consider such patients as being "drug-resistant", we may expect them to have a poorer outcome; however, there is evidence that combined therapies are more effective than psychological therapies alone in the short term (Furukawa 2007), therefore we may also find that such patients have a better outcome compared with patients who are not on drug treatment.

Sensitivity analysis

The process of undertaking a systematic review and meta-analysis involves a sequence of decisions, some of which are somewhat arbitrary or unclear (Higgins 2011). A sensitivity analysis is a repeat of the primary analysis, substituting alternative decisions or range of values for decisions that were arbitrary or unclear. We plan to perform the following sensitivity analyses for the first of the primary outcomes only (short term remission of panic disorder with or without agoraphobia):

- Restrict the inclusion in the analyses only to studies considered to be at low risk of selection and detection bias (i.e. adequate allocation sequence generation, adequate allocation concealment, blinding of assessor).
- Exclude from the analyses group therapy trials.
- Exclude from the analyses trials in which a concomitant pharmacotherapy is allowed.
- Exclude from the analyses trials in which drug therapy is not stabilized*.
- For pair-wise meta-analyses, use a fixed-effect model instead of a random-effects model

(*) Drug therapy will be considered stabilized when: 1) drug administration remains stable before randomizations (for at least 4 weeks in the case of antidepressants and for at least 2 weeks in the case of benzodiazepine and other drugs), and 2) patients are asked to avoid any drug-therapy change for the whole duration of the study.

Summary of findings tables

Aiming at summarizing the results in a way that is as "clinically informative" as possible, we will present the main results in four summary of finding tables.

In the first table we will present the NMA results of the comparison between the face-to-face psychological intervention that ranks first versus the no treatment condition (NT), in order to show the effects of the supposedly most effective treatment when compared to no intervention at all.

In the second table we will present the NMA results of the comparison between the face-to-face psychological intervention that ranks first versus versus supportive psychotherapy (SP), in order to show the effects of the supposedly most effective treatment when compared to a non-specific psychological intervention.

In the third table we will present the NMA results of the comparison between the face-to-face psychological intervention that ranks first versus the one that ranks second, in order to show the magnitude of the effect sizes across the two active interventions that represent the supposedly most viable therapeutic options.

Finally, In the fourth table we will present the NMA results of the comparison between face-to face CBT versus self-help CBT, in order to show the magnitude of the effect sizes between two different formats of delivery of the same psychological intervention.

Since the "waiting list" and "attention/psychological placebo" conditions are useful comparators for clinical trials but do not represent treatment options in a "real" clinical setting, the choice of using the "no treatment" and "psychological support" conditions as comparators is considered by the authors to be more clinically informative.

Declarations of interest

TAF has received honoraria for speaking at CME meetings sponsored by Asahi Kasei, Eli Lilly, GlaxoSmithKline, Mochida, MSD, Otsuka, Pfizer, Shionogi and Tanabe-Mitsubishi. He is diplomate of the Academy of Cognitive Therapy. He has received royalties from Igaku-Shoin, Seiwa-Shoten and Nihon Bunka Kagaku-sha. He is on advisory board for Sekisui Chemicals and Takeda Science Foundation. The Japanese Ministry of Education, Science, and Technology, the Japanese Ministry of Health, Labor and Welfare, and the Japan Foundation for Neuroscience and Mental Health have funded his research projects.

Other authors report no competing interests.

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Appendices

CCDANCTR-References Register Search (Psychotherapies for Panic)

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)

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 (("psychotherapy"[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]))