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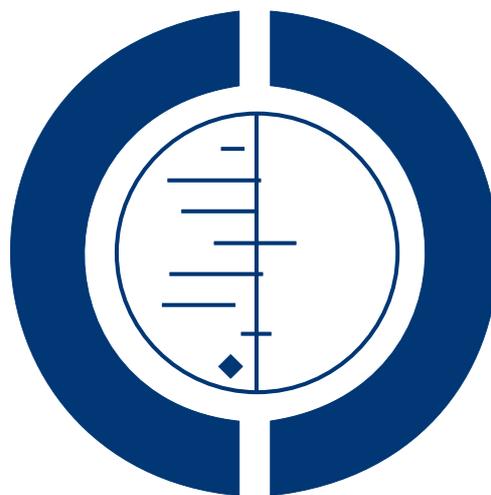
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Cognitive behavioural therapy for anxiety disorders in later life (Protocol)

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[Intervention Protocol]

Cognitive behavioural therapy for anxiety disorders in later life

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

1. To assess the efficacy and feasibility of CBT (CT, BT, CBT and third wave CBT interventions) for different anxiety disorders in older adults aged 55 years or over compared with minimal management
2. To assess the efficacy and feasibility of CBT (CT, BT, CBT and third wave CBT interventions) for different anxiety disorders in older adults aged 55 years or over compared with other psychological therapies
3. To conduct a narrative review to additionally describe trials omitted from the quantitative analysis due to missing data.

BACKGROUND

Description of the condition

Patients with anxiety complain of tension or restlessness, or they exhibit jitteriness, autonomic hyperactivity, vigilance, insomnia, distractibility, shortness of breath, numbness, apprehension, worry or rumination. Although most people experience such symptoms, an anxiety disorder is suspected when symptoms become disproportionately severe compared to their problems. According to the criteria of the Diagnostic and Statistical Manual of Mental Disorders (DSM), anxiety disorders in later life are classified similarly to those in adult life and include panic disorder with and without agoraphobia, generalised anxiety disorder, social phobia, specific phobia, obsessive-compulsive disorder, and post-traumatic and acute stress disorder (APA 1980, APA 1987, APA 1994). Pure anxiety disorders in later life are rare, as most patients have a comorbid second anxiety disorder or depressive disorder (Flint 2005; Kessler 2005a; Lenze 2005; van Balkom 2000).

The prevalence rate of anxiety disorders among older adults living in the community has been estimated between 10 and 15%, with generalised anxiety disorder, panic disorder and specific phobias being the most common (Beekman 1998; Kessler 2005b). In later life, anxiety disorders impair quality of life by having a negative impact on functioning, well-being, and medical consumption (De Beurs 1999; Wetherell 2005b; van Zelst 2006). Moreover, patients suffering from anxiety disorders have an increased risk of becoming depressed (Beekman 2000), and left untreated, anxiety disorders tend to become chronic (Larkin 1992). In two large cohort-studies, anxiety disorders in later life were prospectively associated with an increased mortality rate (van Hout 2004; Brenes 2007).

Description of the intervention

First line treatment for anxiety disorders consist of psychological treatment or antidepressant drugs (van der Velde 2003; NICE 2007). Community studies show that only 5.1% of older adults suffering from anxiety disorders receive psychological treatment and only 3.8% are prescribed an antidepressant drug (De Beurs 1999). Both patient and physician characteristics may contribute to this phenomenon. Many older adults resist the use of antidepressants based on fear of dependence, prior negative experiences, resistance to viewing their symptoms as a medical illness, and concern that antidepressants will prevent natural feelings (Givens 2006). The average duration between anxiety symptom onset and first treatment contact has been shown to be between 9 and 23 years, suggesting general practitioners do not easily recognise anxiety disorders (Wang 2005; Kroenke 2007). The referral rate from primary care to a mental health specialist is three times lower for older adults suffering from anxiety disorders (17%) compared to those suffering from depression (55%) (Ettner 1997). Furthermore, general practitioners themselves may be reluctant to prescribe drugs for

anxiety symptoms being afraid for increased side-effects in later life, for example the increased risk of falling and traffic accidents, memory impairment, and dependency associated with the use of benzodiazepines (Gorgels 2001) and hyponatraemia with the use of serotonin reuptake inhibitors (Wright 2008). Also of concern are the adverse effects of drug interactions, such as gastrointestinal bleeding resulting from the concurrent use of serotonin reuptake inhibitors and non steroidal anti-inflammatory drugs in this age group known for polypharmacy use (Yuan 2006; Weinrieb 2005). As effective management of anxiety disorders in later life may improve outcome, it is important that guidelines for treatment become available.

Cognitive-behavioural therapy (CBT) combines principles of both behavioural and cognitive therapy. Cognitive therapy (CT) assumes that a patient's symptoms (e.g., anxiety) arise from misperceptions and attitudes about the world and themselves (Beck 1995). Behavioural therapy (BT) is a directive, active approach involving principles of learning to help the patient develop new and adaptive ways of behaving (Bandura 1969; Yates 1970). As a psychotherapy, CBT is characterised as a structured, goal-oriented, problem-focused, time-limited intervention (Korrelboom 2004).

In order to deal with age-associated cognitive impairment, some authors argue for inclusion of learning and memory aids like homework reminders, troubleshooting calls or weekly review of all concepts and techniques (Mohlman 2003). Recent RCTs on older adults, however, remain inconclusive on whether age-related adaptations of psychotherapeutic techniques are necessary to remain efficacious for anxiety disorders in later life (Stanley 2003a; Stanley 2003b; Wetherell 2005a).

How the intervention might work

CBT identifies habitual ways in which patients distort information (e.g., automatic thoughts) and teaches patients to identify and respond to their dysfunctional thoughts and beliefs, using a variety of techniques to change thinking, mood, and behavior. Behavioural interventions help the patient develop new and adaptive ways of behaving. Exposure based treatment utilises gradual, systematic, repeated exposure to the feared object or situation to desensitise patients with anxiety disorders to the feared stimulus. The controlled exposures are predictable and the patient is taught a variety of adaptive coping strategies.

Why it is important to do this review

CBT is generally considered the most effective psychotherapy for anxiety disorders (van der Velde 2003). The efficacy of CBT for anxiety disorders in young and middle-aged adults is supported by a variety of meta-analyses (Bakker 1998; Mitte 2005a; Furukawa 2006; Mitte 2005b; Westen 2001). However, whether these re-

sults also apply to older adults remain unclear since most trials exclude participants over the age of 65 years (Wetherell 2003). Generalisation of meta-analytic studies in young and middle-aged adults to older adults is limited, as older adults often have more chronic disorders, which are presumed to be more treatment resistant (Katz 2002). Therefore, the current review aims to provide a comprehensive and up to date summary of the available evidence on CBT as a treatment for older adults.

Many of the earlier studies regarding the psychological treatment of anxiety disorders in later life suggest efficacy for CBT, but have been limited to subclinical anxiety and lack rigorous inclusion criteria, like the presence of an anxiety disorder according to diagnostic guidelines (Nordhus 2003). Recent reviews generally conclude psychological treatment is effective for anxiety disorders in later life, but also conclude that there is a need for large, rigorous controlled trials for the different anxiety disorders (Nordhus 2003; Pinquart 2007; Ayers 2007). However, in later life, pure anxiety disorders are rare, as most patients have a comorbid second anxiety disorder or depressive disorder. For the purposes of conducting the current review, therefore, generalised anxiety disorder, panic disorder with and without agoraphobia and social phobia, conditions that often overlap, will be combined into one single diagnostic category called anxiety disorders. Obsessive-compulsive disorder and the stress disorders, acute and post-traumatic stress disorder, will be considered as separate diagnostic categories.

OBJECTIVES

1. To assess the efficacy and feasibility of CBT (CT, BT, CBT and third wave CBT interventions) for different anxiety disorders in older adults aged 55 years or over compared with minimal management
2. To assess the efficacy and feasibility of CBT (CT, BT, CBT and third wave CBT interventions) for different anxiety disorders in older adults aged 55 years or over compared with other psychological therapies
3. To conduct a narrative review to additionally describe trials omitted from the quantitative analysis due to missing data.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled trials (RCTs) will be included. In the case of cross-over trials (a rare feature within this field of research),

only the first randomisation period will be included in the review. Studies using a quasi-randomised design will be excluded. Cluster RCTs, in which centres or therapists were randomised to intervention or control groups will be included, provided that the specific aim of the study was to examine the effect of the intervention.

Types of participants

All RCTs of older people (55 years or older) with a primary diagnosis of an anxiety disorders according to DSM-III (APA 1980), DSM-III-R (APA 1987), DSM-IV (APA 1994), ICD-9 (ICD-9 1979), ICD-10 (ICD-10 1999) diagnostic criteria will be considered for inclusion, irrespective of culture and setting.

The review will combine generalised anxiety disorder, panic disorder with and without agoraphobia and social phobia, conditions that often overlap, into one single category called anxiety disorders. Obsessive-compulsive disorder (OCD) and the stress disorders, acute and post-traumatic stress disorder, will be considered separately. OCD is often hypothesised to be part of an obsessive-compulsive symptom spectrum, including body dysmorphic disorder, hypochondriasis, eating disorders, tic disorders and autism (Bartz 2006). Moreover, OCD is more treatment resistant compared to other anxiety disorders, and pharmacological treatments may be different from the other anxiety disorders, since they include the use of antipsychotics where there is treatment resistance and benzodiazepines are not effective agents (Bandelow 2008; van der Velde 2003). Posttraumatic stress disorder and acute stress disorder is reviewed and analysed separately due to its causal relationship with psycho-traumatic events prior to the onset of the disorder. A similar distinction is made by International Classification of Diseases (ICD-9 1979; ICD-10 1999), acknowledging four categories of anxiety disorders, namely 1) phobic anxiety disorders, 2) other anxiety disorders (together comparable to our category 'anxiety disorders'), 3) obsessive-compulsive disorders and 4) reaction to severe stress and adjustment disorders. For the purposes of this review, the three anxiety disorder categories (anxiety disorders, OCD and PTSD) will be stratified in analyses.

Of studies that include both the target population and younger participants, the relevant data will be included on the condition that randomised age blocks have been used and data are reported in age-blocks.

Studies concerning anxiety symptoms that are part of the clinical presentation of another primary diagnosis (e.g. substance use disorders, major depression) will be excluded, as well as studies involving patients with a comorbid psychiatric diagnosis of substance-related disorder, schizophrenia or psychotic disorder. However, studies involving participants with comorbid physical illnesses will be eligible for inclusion to increase generalisability, as most older people suffer from physical illnesses.

Types of interventions

Experimental intervention

Cognitive therapy (CT) is defined as cognitive restructuring of irrational and maladaptive anxiety beliefs. Behavioural therapy (BT) is defined as some form of exposure and/or relaxation exercises. Cognitive-behavioural therapy (CBT) is defined as delivering a combination of both CT and BT. In studies where behavioural experiments are included, the therapy will be considered to be CBT, because behavioural experiments are exercises of new behaviour (BT) designed to challenge irrational or maladaptive beliefs (CT). Studies including 'third wave' CBT interventions (e.g. mindfulness, acceptance and commitment therapy) will also be included. A minimum number of six therapy sessions has to be delivered, either in an individual or group format.

Comparator interventions

Non-CBT psychological therapies and minimal management will be included as control interventions. Non-CBT psychological therapies include non-directive (supportive) therapies, psychodynamic therapy and interpersonal psychotherapy. Minimal management (also sometimes described in trials as standard care, treatment as usual or waiting list), is defined as being elements of clinic attendance, investigation, reassurance, and simple advice, without explicit psychological therapy, and also may include naturalistic prescribing of medication and/or other interventions.

Combination therapy

CBT in combination with pharmacological treatment will be excluded, as its superior effects over the monotherapies (van Balkom 1997; Bakker 1998) have been challenged by recent meta-analyses (Furukawa 2006; Mitte 2005a; Mitte 2005b).

Main comparisons

1. CBT, stratified as CBT, BT, CT and third wave CBT interventions versus minimal management
2. CBT, stratified as CBT, BT, CT and third wave CBT interventions versus all non-CBT psychological therapies

Types of outcome measures

Primary outcomes

The principal outcome used in this review will be anxiety, measured as follows:

1. Reduction in anxiety severity (continuous), measured by a well-validated, observer rated instrument like the Hamilton Rating Scale for Anxiety (Hamilton 1959), or if not available, a well validated self-report instrument measuring general anxiety like the Beck Anxiety Inventory (Beck 1988a). Validated disorder-specific instruments for obsessive-compulsive disorder or posttraumatic stress disorder will be used.
2. Clinical recovery or improvement (dichotomous), based on diagnostic interview or defined cut-off on validated scales, as specified by trial authors. In case the Clinical Global Impression scale [change item] (CGI-C) is used, responders are defined as having a change score of 1 = 'very much' or 2 = 'much' improved (Guy 1976).

Secondary outcomes

The following secondary outcome measures will included in the review:

1. Worrying, assessed continuously by well-validated, self-report questionnaires, like the Penn State Worrying Questionnaire (Meyer 1990; van Rijsoort 1999).
2. Depression, assessed continuously by well-validated, self-report questionnaires, like the Beck Depression Inventory (Beck 1988b).
3. Anxiety, assessed continuously by well-validated observer-rated or self-report questionnaires, in studies of obsessive-compulsive disorder or posttraumatic stress disorder
4. Dropout rate will be included as a surrogate measure of feasibility of cognitive-behavioural therapy, in lieu of other more direct indicators of feasibility.
5. Occurrence of adverse events
6. Quality of life, assessed continuously by well-validated, self-report questionnaires, like the SF-36 (Ware 1992).

Search methods for identification of studies

A number of sources will be used to identify studies for possible inclusion in this review (see below). Studies will not be limited to any particular language.

Electronic searches

The Cochrane Collaboration Depression, Anxiety and Neurosis Controlled Trials Register (CCDANCTR) will be searched using the following terms:

CCDANCTR-Studies

Diagnosis = Anxiety or Anxious or Phobi* or Panic or Obsess* or Compulsi* or Post-Traumatic and Age-Group = Aged and Intervention = *Therapy

CCDANCTR-References

Keyword = Anxiety or Anxious or *phobi* or "Panic Disorder" or "Obsessive Compulsive Disorder" or "Post-Traumatic Stress Disorders and Free-text = Elder* or Geriatri* or Senil* or Older or "Old Age" or "Late Life" or "Aged, 80-And-Over"

A search of PubMed and of PsycINFO (which includes Dissertation Abstracts Internal, a database of unpublished dissertations) will also be conducted. The following keywords will be used "late-life", "Elderly", "Aged", "Aged, 80 years and over", "Old Age", "Anxiety disorder", "Anxiety", "Panic", "Agoraphobia", "Phobia", "Obsessive-compulsive", "Posttraumatic", "psychotherapy", "cognitive therapy", "behavior therapy", "cognitive behavior therapy". See Appendix 1 for the exact search strings that will be used in the different databases.

Searching other resources

Correspondence

Experts in this field and principal authors who have published controlled trials in the field of late-life anxiety will be asked if they know of any study which meets the inclusion criteria of this review.

Reference lists

Citation lists of potentially relevant papers obtained by these methods will be searched for further relevant trials, as will be the reference lists of those further relevant trials. In addition, the citation lists of relevant and recent systematic reviews were perused.

Data collection and analysis

Selection of studies

RCTs that have been identified will be independently assessed for inclusion by two review authors (RCOV & GJH), based on information included in the abstract and/or main body of the trial report. RCTs that both raters regard as satisfying the inclusion criteria specified in the "Criteria for selecting studies" section will be collated by the raters (see above). If the raters disagree, the final rating will be made by consensus, if necessary with the involvement of another member of the review group (AJLMvB). Non-congruence in selection of trials will be reported as percentage disagreement. Considerable care will be taken to exclude duplicate publications.

Data extraction and management

Spreadsheet forms will be designed for the purpose of recording descriptive information, summary statistics of the outcome measures, the quality scale ratings, and associated commentary. These data will then be exported to RevMan. Where information is missing, the reviewers will contact investigators by letter or email in an attempt to obtain it.

The following data will be extracted from each trial by two review authors independently (RCOV & GJH):

1. Description of the trials, including primary researcher and year of publication.
2. Characteristics of the interventions, including the number of participants randomised to CBT-condition and control groups, therapy-characteristics, including, the number of sessions provided, groups versus individual therapy, and components of the therapy (psycho-education, relaxation training, anxiety management, type(s) of exposure, cognitive techniques, and behavioural experiments), and finally the classification in CT, BT, CBT or third wave CBT interventions.
3. Characteristics of trial methodology, including the diagnostic and exclusion criteria employed, the screening instrument used, the inclusion of comorbidity, a minimal severity criterion, and the number of centres involved.
4. Characteristics of participants, including their gender distribution, mean age, and the duration of primary symptoms.

5. Outcome measures employed, and summary continuous (means and standard deviations) and dichotomous (number of responders) data. Additional information will be included, such as whether the data reflected the intent-to-treat (ITT) with either last observation carried forward (LOCF), or completer/observed cases (OC) sample, and the dropout rates of participants randomised to the experimental and control groups.

Assessment of risk of bias in included studies

Risk of bias will be assessed for each included study using the Cochrane Collaboration 'risk of bias' tool. The following six domains will be considered:

1. Sequence generation: Was the allocation sequence adequately generated?
2. Allocation concealment: Was allocation adequately concealed?
3. Blinding of participants, personnel and outcome assessors for each main outcome or class of outcomes: Was knowledge of the allocated intervention adequately prevented during the study?
4. Incomplete outcome data for each main outcome or class of outcomes: Were incomplete outcome data adequately addressed?
5. Selective outcome reporting: Are reports of the study free of suggestion of selective outcome reporting?
6. Other sources of bias: Was the study apparently free of other problems that could put it at a high risk of bias?

A description of what was reported to have happened in each study will be provided, and a judgement on the risk of bias will be made for each domain within and across studies, based on the following three categories:

- A. Yes (low risk of bias)
- B. Unclear
- C. No (high risk of bias).

Two independent review authors (RCOV & GJH) will assess the risk of bias in selected studies. Any disagreement will be discussed with a third review author (AJLMvB). Where necessary, the authors of the studies will be contacted for further information.

Measures of treatment effect

Dichotomous outcomes

These outcomes will be analysed by calculating a pooled relative risk (RR) for each comparison, with 95% confidence intervals. Where overall results are significant, the number-needed-to-treat (NNT) to produce one outcome will be calculated.

Continuous outcomes

Anticipating different measures across studies, data will be pooled by calculating the standardised mean difference (SMD), using 95% confidence intervals.

Unit of analysis issues

Where studies have two relevant experimental conditions to be compared against a control condition, data will be managed as follows:

Continuous data - means, SDs and number of participants for each experimental condition will be pooled across the two conditions as a function of the number of participants in each condition (Law 2003) to be compared against the control condition.

Dichotomous data - active treatment groups will be collapsed into a single arm for comparison against the control group, or the control group will be split equally into two.

A similar approach will be used where studies have two relevant control conditions (e.g. usual care and a waiting-list control condition) to be compared against one experimental condition.

Dealing with missing data

Missing dichotomous data will be managed through intention to treat (ITT) analysis, in which it will be assumed that patients who dropped out after randomisation had a negative outcome. Best/worse case scenarios will also be calculated for the clinical response outcome, in which it will be assumed that dropouts in the active treatment group had positive outcomes and those in the control group had negative outcomes (best case scenario), and that dropouts in the active treatment group had negative outcomes and those in the control group had positive outcomes (worst case scenario), thus providing boundaries for the observed treatment effect.

Missing continuous data will either be analysed on an endpoint basis, including only participants with a final assessment, or analysed using last observation carried forward to the final assessment (LOCF) if LOCF data were reported by the trial authors. Where SDs are missing, attempts will be made to obtain these data through contacting trial authors. Where SDs are not available from trial authors, they will be calculated from t-values, confidence intervals or standard errors, where reported in articles (Deeks 1997a; Deeks 1997b). If these additional figures are not available or obtainable, the study data will not be included in the comparison of interest.

Assessment of heterogeneity

Statistical heterogeneity will be formally tested using the natural approximate chi-square test, which provides evidence of variation in effect estimates beyond that of chance. Since the chi-squared test has low power to assess heterogeneity where a small number of participants or trials are included, the p-value will be conservatively set at 0.1. Heterogeneity will also be tested using the I^2 statistic, which calculates the percentage of variability due to heterogeneity rather than chance, with I^2 values over 50% indicating strong heterogeneity (Higgins 2008).

Assessment of reporting biases

Where sufficient numbers of trials allow a meaningful presentation, funnel plots will be constructed to establish the potential influence of publication bias.

Data synthesis

Data will be entered into RevMan 5.0 software by two review authors (double data entry). A fixed effect model will be used in the first instance to combine data. If there is evidence of statistical heterogeneity, results will be recalculated using a random effects model, in order to obtain a more conservative estimate.

Subgroup analysis and investigation of heterogeneity

Multiple subgroup analyses will be performed, but interpreted with caution, due to the risk of false positive conclusions. If possible, the following subgroup analyses will be performed:

1. Separate anxiety disorders (category 1), stratified as generalised anxiety disorder, panic disorder and social phobia.
2. Minimal management control condition (waiting list versus other minimal management control conditions)
3. Other psychological therapy control conditions, stratified as psychodynamic, interpersonal and supportive therapies
4. CBT versus third wave CBT interventions
5. Group versus individual treatment delivery
6. The age classification of participants (55-79 years versus 80 years and over).

Where there are sufficient studies, these subgroup analyses will also be used to examine potential sources of clinical heterogeneity.

Sensitivity analysis

Sensitivity analyses will also be undertaken to assess the degree to which the effect sizes depend on the assumptions made by the reviewers. Studies will be limited to those of higher quality as determined by risk of bias domains, including:

1. Allocation concealment
2. Dropout rate lower than 20%
3. Use of formal testing of fidelity to psychological therapy manual
4. Use of blinded outcome assessors

These sensitivity analyses will also be used to examine potential sources of methodological heterogeneity.

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* Indicates the major publication for the study

APPENDICES

Appendix I. Search strategies

The following search strings will be used:

For the CCDANCTR-Studies database: Keyword="late-life" OR "Elderly" OR "Aged" OR "Old Age" AND Keyword="Anxiety" OR "Panic" OR "Agoraphobia" OR "Phobia" OR "Obsessive-compulsive" OR "Posttraumatic" AND Keyword="psychological therapy" OR "psychotherapy" OR "cognitive therapy" OR "behavio(u)r(al) therapy" OR "cognitive-behavio(u)r(al) therapy" OR "CBT"

For PubMed: Keyword="Aged [MESH]" OR "Aged, 80 years and over [MESH]" AND keyword="Anxiety disorder [MESH]" AND Keyword="behaviour therapy [MESH]"

For PsycINFO: Keyword="late-life" OR "Elderly" OR "Aged" OR "Old Age" AND Keyword="Anxiety disorder [Thesaurus]" AND Keyword="cognitive therapy [Thesaurus]" or "psychotherapy [thesaurus]" OR "cognitive behavior therapy [Thesaurus]" OR "behavior therapy [Thesaurus]"

WHAT'S NEW

Date	Event	Description
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Dr R.C. Oude Voshaar and Dr. G.J. Hendriks have written the first draft in close collaboration. Dr. G. Keijsers and Prof. dr. A.J.L.M. van Balkom have commented on the draft for important intellectual content.

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