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[Intervention Protocol]

The process and delivery of cognitive behavioural therapy (CBT) for depression in adults: a network meta-analysis

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To assess the comparative efficacy and tolerability of different content and delivery cognitive behavioural therapy (CBT) components, and combination of components of CBT for the treatment of depression in adults using a component-level network meta-analysis.

BACKGROUND

Description of the condition

Major depressive disorder is one of the most common forms of mental disorder and is characterised by low mood and a diminished interest in pleasurable activities. Individuals can experience a range of symptoms including weight loss or weight gain, a decrease or increase in appetite, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue, loss of energy, diminished concentration or ability to think, feelings of worthlessness or of inappropriate guilt, disruptions to decision making, and morbid thoughts of death (APA 2013).

The global burden of depression has risen greatly over the past few decades, and it is now estimated that 350 million people worldwide are affected by the disorder (World Health Organization

2016). As the leading cause of disability worldwide (World Health Organization 2016), depression is associated with marked personal, social and economic morbidity, loss of functioning and productivity, and high levels of service use (NICE 2009).

Description of the intervention

Cognitive behavioural therapy (CBT) is the most commonly researched psychological therapy for the treatment of depression (Hofmann 2008). CBT can be regarded as a 'family' of related therapies (Mansell 2008), and may be delivered in many forms. Treatment protocols variously incorporate a range of different components such as psychoeducation, cognitive restructuring, behavioural activation, and problem solving. These may be used alone or in multiple combinations, often depending on patient formulation. Evidence suggests that CBT is an efficacious treat-

ment for depression and its use is recommended by the National Institute for Health and Care Excellence (NICE 2009).

As a family of complex interventions consisting of various therapeutic components, CBT can be delivered in a number of ways. Whilst more usually provided in a traditional face-to-face setting (as either individual or group therapy), CBT can also be delivered with via multi-media platforms. Multi-media delivered CBT can be defined as any standardised CBT approach that is delivered using one, or a combination of, the following multimedia platforms: self-help books, audio or video recordings, telephone, computer programmes (both online and desktop), Apps, e-mail, or text messages. These therapies can be provided with varying amounts of therapist interaction. Some approaches defined as 'self-help' are designed to be completed almost entirely independent of professional contact, with the individual working through the therapy programme at their own pace with only technical help provided (Bower 2001). In guided self-help CBT, an individual is given access to a standardised CBT programme and works through it more or less independently but with support provided by a therapist. The support tends to be of supportive or facilitative nature, and is meant to support the patient in working through the CBT programme (Cuijpers 2010). In guided self-help CBT, the interaction between patient and therapist can take place by telephone, email, text message, or any other communication method. More recently, blended treatments have been developed with the aim of preserving the personal contact and therapeutic relationship that occurs in traditional face-to-face therapy, whilst maintaining the benefits of increased accessibility that come with multi-media delivered therapies (Kenter 2015; Kooistra 2016). Blended programmes combine real-time therapist interaction - conducted either face-to-face or remotely - with multi-media delivered material to form one treatment (e.g. Hoifodt 2013; Kessler 2009; Månsson 2013).

How the intervention might work

CBT is based on Beck's cognitive model of depression (Beck 1976). The model proposes that problematic experiences in early life can make an individual vulnerable to depression through the development of negative core beliefs about the self, others and the world. These core beliefs can be triggered later in life by stressful events. During episodes of depression, information processing is affected, leading to biased and negative interpretation of interpersonal experiences, with an increased sense of isolation and reduced levels of activity (Grant 2004).

Cognition is central to the treatment of depression in CBT, with emotions and behaviour thought to be mediated by cognitive processes. CBT approaches are based on three fundamental propositions that cognitive activity affects behaviour, that cognitive activity can be monitored and altered, and that desired behaviour change may be affected through cognitive change (Dobson 2001). In CBT, therapists work collaboratively with individuals to help

them identify, explore and modify relationships between negative thinking, behaviour and depressed mood. This is achieved by learning to identify and monitor the intensity of different moods, recognising the thoughts and behaviours that have contributed to this mood, and learning how to address these by evaluating and challenging unhelpful thoughts and engaging in behaviour that contributes to improved mood. Cognitive change in depression is achieved by targeting negative automatic thoughts (immediate and plausible negative thoughts based on faulty schema that are not arrived at through reflective reasoning) using techniques such as thought catching, reality testing, task assignment and generating alternative strategies (Williams 1997). Behavioural experiments are then used to re-evaluate underlying beliefs and assumptions (Bennett-Levy 2004).

Why it is important to do this review

Currently there is little understanding about which components, combinations of components, and modes of delivery are the most effective at reducing depression. It is possible that treatment effects are yielded by a certain components beyond which the addition of other components might add little or no benefit. Attempts to assess the efficacy of different components/combinations of components of CBT for depression have largely taken the form of dismantling studies (Christensen 2006; Jacobson 1996; Vázquez 2015), where one group of individuals receive a particular CBT component or combination of components, and are compared with an alternative combination. In this design, two combinations of components can be directly compared.

The aim of this review is to compare the efficacy and tolerability of components and combinations of components - commonly used in CBT - and delivered via a range of platforms, using a component level network meta-analysis (NMA). NMA (also known as 'Multiple treatment meta-analysis' or 'Mixed Treatment Comparisons') is a form of meta-regression that facilitates the concurrent comparison of multiple interventions in a single analysis. Using a connected network, this statistical strategy allows all pairwise effects to be estimated, even in the absence of direct evidence, while at the same time respecting the randomisation of the evidence (Bucher 1997). NMA has been extended and used successfully to estimate the relative effectiveness and acceptability of different process and content components, and combinations of components of interventions, by fitting additive and interaction models (Caldwell 2016; Welton 2009a). In this review, we plan to categorise components and combinations of components of CBT for depression by using a method adapted from other reviews involving qualitative assessment of the intervention information provided in the trial reports (Faggiano 2008; Hetrick 2015). We will then complete a NMA at the component level.

OBJECTIVES

To assess the comparative efficacy and tolerability of different content and delivery cognitive behavioural therapy (CBT) components, and combination of components of CBT for the treatment of depression in adults using a component-level network meta-analysis.

METHODS

Criteria for considering studies for this review

Types of studies

Clinical characteristics of included studies have been chosen to reflect, as far as possible, the context in which CBT is actually delivered.

We will include randomised controlled trials (RCT); cluster-randomised trials; and though an unlikely methodology to use in this area, we will also include any cross-over trials. For cross-over trials, only the results of the first active treatment phase will be included in our analysis.

Types of participants

Participant characteristics

Adults between 18 and 74 years will be included (studies that include adults above 74 years of age will be included where the average age is 74 or below). A broad age range has been chosen to reflect the age group likely to be offered CBT for their depression. The increasing prevalence of memory decline (Ivnik 1992), cognitive impairment (Rait 2005) and multiple comorbid physical disorders/polypharmacy (Chen 2001) in individuals over 74 years may differentially influence the process and effect of psychological therapy interventions, especially those delivered via a multimedia format. The effects of different components and different methods of delivery in individuals over 74 are deserving of a standalone review.

Diagnosis

We will include studies of participants receiving treatment during an acute phase of depression. The acute phase could be a first episode, or a relapse.

1. Studies adopting any standardised diagnostic criteria to define participants suffering from an acute phase unipolar depressive disorder will be included. Accepted diagnostic criteria include Feighner criteria, Research Diagnostic Criteria, DSM-III

(APA 1980), DSM- III-R (APA 1987), DSM-IV-TR (APA 2000), DSM-5 (2013) or International Classification of Diseases (ICD-10) (WHO 1992) criteria.

2. In order to fully represent the broad spectrum of severity of depressive symptoms encountered in outpatient/ primary care settings (Mitchell 2009; Rait 2009; Roca 2009), studies that use non-operationalised diagnostic criteria, or a validated depression symptom questionnaire to identify depression based on a recognised threshold will also be included. Studies using both clinician-rated (e.g. Hamilton Rating Scale for Depression (Hamilton 1960)) or participant-rated (e.g. Beck Depression Inventory (Beck 1961)) symptom questionnaires will be eligible for inclusion. The influence of including studies that use a non-operationalised diagnostic criteria will be examined in a sensitivity analysis.

Co-morbidities

Studies involving participants with comorbid physical or common mental disorders will be eligible for inclusion, as long as the comorbidity is not the focus of the study. For example, we will exclude studies that focus on depression among patients with Parkinson's disease or after acute myocardial infarction, but will accept studies that may have included some participants with Parkinson's disease or with acute myocardial infarction.

Setting

Studies may be conducted in primary care and community-based settings, or in secondary or specialist settings, and will include referrals as well as volunteers. Studies involving inpatients will be excluded. Studies that focus on specific populations - nurses, care givers, depressed participants at a specific work place - will be included if the participants all meet the criteria for depression.

Types of interventions

We will include in our network studies that compare the following, broadly categorised, interventions.

1. Face-to-face CBT: provided in either an individual or group format.

2. Multi-media delivered CBT: we define multi-media delivered psychological therapy as any standardised CBT approach that is delivered via one, or more of the following multimedia platforms: self-help books, audio or video recordings, telephone, computer programmes (both online and desktop), apps, e-mail, or text messages. Multi-media delivered therapies can be provided with varying amounts of therapist interaction broadly defined as self-help, guided self-help, and blended treatment.

- i) Self-help CBT: individuals work through the CBT programme entirely independently, or with only minimal help provided where necessary regarding technical aspects such as

navigating the programme. These treatments are most likely to be delivered via self-help books, audio or video recordings, or computer programmes.

ii) Guided self-help: individuals receive some level of guidance from clinical practitioners. This guidance could be in the form of e-mail or text message reminders, assessment of homework via e-mail, or scheduled telephone calls.

iii) Blended CBT: integrated delivery of CBT through a mixture of real-time therapist contact and multi-media delivered materials. Real-time therapist contact could be conducted face-to-face or remotely (e.g. via Skype, or instant messaging).

3. Treatment as usual: in each study, descriptions of 'treatment as usual' and attention placebo conditions will be scrutinised to ensure that they do not comprise an active psychological therapy treatment. Comparators will be subgrouped as follows.

i) Usual care or no treatment (UC).

ii) Waiting list (WL); participants receive assessment at the point of randomisation and are told that they will receive the active treatment after waiting for a specific duration.

iii) Attention placebo (AP); any form of inactive intervention designed by the original authors to be perceived as ineffective by patients.

iv) Psychological placebo (PP); 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 the intervention to be inactive.

Within the 'treatment as usual' and waiting list conditions, participants may receive any appropriate medical care during the course of the study on a naturalistic basis, including pharmacotherapy and/or psychological therapy, as deemed necessary by the clinician.

Participants within the active treatment arms of the trials may receive anti-depressant medication on a naturalistic basis, however we will exclude studies where combination treatment is provided. Any additional treatment in both the active and control conditions for each included study will be documented.

Identification of intervention components

Components are the active ingredients of interventions, and can be considered at both a content and process/ delivery level. We will use the constant comparative method (CCM) to identify components of CBT interventions described in the CBT for depression literature (Hetrick 2015). CCM is an iterative and inductive process of reducing data into common categories or themes through constant recoding. We will apply CCM to published trial reports and accompanying process evaluations, coding the components, or combination of components involved. As such, it is not possible to specify components in advance, however, examples may include a cognitive or behavioural activation content component and a face-to-face or computer-delivered format. Identified components

will be discussed with a panel of clinical psychologists, therapists and clinicians to arrive at an agreed nomenclature and to generate a final taxonomy for components of CBT interventions. The taxonomy will be reported in the main review.

Types of outcome measures

We will estimate the relative ranking of the intervention, intervention components, or combinations of components where possible, according to the primary outcomes:

Primary outcomes

1. Treatment efficacy: the number of patients who respond to treatment, based on changes on Beck Depression Inventory (BDI) (Beck 1961), Hamilton Rating Scale for Depression (HAM-D) (Hamilton 1960) or Montgomery-Asberg Depression Rating Scale (MADRS) (Montgomery 1979), or any other validated depression scale. Many studies define response by 50% or greater reduction on BDI, HAM-D etc. but some studies define response using Jacobson's Reliable Change Index; we will accept the study authors' original definition. If the original authors report several outcomes corresponding with our definition of response, we will give preference to BDI for self-rating scale and HAM-D for observer-rating scale.

2. Treatment acceptability: the number of participants who drop out of treatment for any reason.

Secondary outcomes

1. The number of patients who achieve remission. Remission status will be assessed based on the endpoint status of participants, as measured using the BDI (Beck 1961), BDI-II (Beck 1996), HAM-D; (Hamilton 1960) or MADRS; (Montgomery 1979), or any other validated depression scale. Examples of definitions of remission include 10 or less on BDI, seven or less on HAM-D or 10 or less on MADRS; we will accept and record study authors' definitions of remission.

2. Improvement in depression symptoms as measured by a change in depression scores using the DSM-IV-TR (APA 2000) or ICD-10 (WHO 1992) or other validated diagnostic instruments, for example HAM-D (Hamilton 1980), BDI-II (Beck 1996), Hospital Anxiety and Depression Scale (HADS) (Zigmond 1983) and Geriatric Depression Scale (GDS) (Sheikh 1986).

3. Adverse events as reported by the authors, including incidence of self-harming behaviour, completed suicide, attempted suicide, and worsening of behaviour.

4. Quality of life measured using validated measures such as the EQ-5D (EuroQol group 1990) SF-36 (Ware 1993), Health of the Nation Outcome Scale (HoNOS; Wing 1998) and The World Health Organization Quality of Life (WHOQL 1998).

Timing of outcome assessment

We will extract outcomes measured post-treatment and at follow-up. We will categorise outcomes as short term (up to six months post-treatment), medium term (seven to 12 months post-treatment), and long term (longer than 12 months post-treatment). When authors measure outcomes at multiple time points within a pre-defined period, we will include only the longest time point after randomisation.

Hierarchy of outcome measures

When several possible outcome measures are reported for the same outcome, we will use the primary outcome according to the original study.

Search methods for identification of studies

Electronic searches

We will search MEDLINE (1950-), Embase, (1974-), PsycINFO (1967-) and the Cochrane Central Register of Controlled trials (CENTRAL) via the specialised register of the Cochrane Common Mental Disorders Group (CCMDCTR) to 10-June-2016. This register contains over 40,000 reports of RCTs for common mental disorders, collated from repeat, generic searches of the core biomedical databases (a search based on Population and RCT filter only) (Appendix 1). For the purpose of this network meta-analysis, we will include studies identified from three separate searches of the CCMDCTR, for a suite of Cochrane reviews (Churchill 2013; Hunot 2010; Hunot 2013). Each search will use a sensitive list of terms for intervention (Appendix 2).

We will run additional searches of Ovid MEDLINE, Embase, PsycINFO and the Cochrane Central Register of Controlled Trials (CENTRAL) (directly) from 2016 onwards, to complement the searches of the CCMDCTR.

We will not apply any restrictions on date, language or publication status to the searches.

We will search International trial registries via the World Health Organization's trials portal (ICTRP) and ClinicalTrials.gov to identify unpublished or ongoing studies.

Searching other resources

Reference lists

We will check the reference lists of all included studies and relevant systematic reviews to identify additional studies missed from the original electronic searches (for example unpublished or in-press citations).

Correspondence

We will contact trialists and subject experts for information on unpublished or ongoing studies or to request additional trial data.

Data collection and analysis

Selection of studies

Two review authors will independently assess titles and abstracts for relevance. We will code abstracts as 'retrieve' or 'do not retrieve'. We will then find the full-text papers for all abstracts coded retrieve. The full-text papers will be assessed for inclusion independently by two review authors. Conflicts will be resolved through discussion, or by consultation with a third review author. Reasons for exclusion will be noted. Multiple reports of the same study will be tagged together. We will record the study selection in sufficient detail to produce a PRISMA flow diagram.

Data extraction and management

We will extract from each study the number of participants who responded to treatment as measured using the BDI ((Beck 1961), (HAM-D) (Hamilton 1960) or MADRS (Montgomery 1979), or any other validated depression scale. We will also extract the number of participants and the number of dropouts; the number of participants classed as having achieved remission; change in depression symptom scores measured using the DSM-IV-TR (APA 2000) or ICD-10 (WHO 1992) or other validated diagnostic instruments, for example HAM-D (Hamilton 1980), BDI-II (Beck 1996), HADS (Zigmond 1983) and GDS (Sheikh 1986); adverse events; and quality of life measured by EQ-5D (EuroQol group 1990) SF-36 (Ware 1993), Health of the Nation Outcome Scale (HoNOS; Wing 1998) and The World Health Organization Quality of Life (WHOQL 1998).

Data on potential effect modifiers

We will extract the following study, intervention and population characteristics from each study as they may act as effect modifiers.

1. Baseline symptom severity
2. Gender
3. Participant age
4. Duration of treatment
5. Length of follow up
6. Proportion of participants with comorbidities
7. Year of trial publication
8. Number of previous episodes of depression
9. Antidepressant use

At least two review authors will independently extract data from all included studies using a structured excel data collection form. Any disagreements in the extraction process, including determining the constituent components of the interventions, will be resolved by consultation with a third member of the author team.

Assessment of risk of bias in included studies

Two review authors will independently assess the risk of bias of the included trials using the approach described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Any disagreements will be resolved either through discussion or by consulting a third author. We will assess the risk of bias according to the following domains.

1. Random sequence generation
2. Allocation concealment
3. Blinding of participants and personnel
4. Blinding of outcome assessment
5. Incomplete outcome data
6. Selective outcome reporting
7. Other bias

We will judge each potential source of bias as high, low, or unclear and provide a supporting quotation from the study report together with a justification for our judgement in the 'Risk of bias' table. We will assess blinding for outcome assessment separately for objective-rated outcomes and those rated subjectively.

We will judge each potential source of bias as high, low, or unclear and provide a supporting quotation from the study report together with a justification for our judgement in the 'Risk of bias' table. We will assess blinding for outcome assessment separately for objective-rated outcomes and those rated subjectively.

Measures of treatment effect

Continuous outcomes

Where studies use the same outcome measure for comparison, data will be pooled by calculating the mean difference (MD), or standardised mean difference (SMD) if values across trials on the same scales vary greatly. When different measures are used to assess the same outcome, data will be pooled using the SMD, or we will map between outcomes using the approach described by (Ades 2015). We will also calculate and report 95% confidence intervals (95% CIs).

Dichotomous data

Dichotomous outcomes will be analysed where possible by calculating using a pooled odds ratio (OR). We will also calculate and report 95% CIs.

Unit of analysis issues

Cluster-randomised trials

We will include cluster-randomised trials only if the intracluster correlation coefficient (ICC) is reported or can be borrowed from

similar trials. We will estimate the effect size in cluster-randomised trials using the ICC to adjust for cluster effects as described in the *Cochrane Handbook for Systematic Reviews of Interventions*, section 16.4.3 (Higgins 2011).

Cross-over trials

Cross-over trials will only be included in the calculation of summary statistics when it is possible to extract intervention and comparator data from the first treatment period.

Dealing with missing data

In the case of missing outcome data, we will contact study authors to request the relevant data. Where authors are unable to provide the information, we will impute the missing values as follows.

Dichotomous outcomes

Missing dichotomous data will be managed assuming that patients who dropped out after randomisation had a negative outcome i.e. non-response. Best-/worse-case sensitivity analyses will also be conducted e.g. assuming 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. If there is a large amount of missing information then these best-/worst-case scenarios will be given greater emphasis in the presentation of the results.

Continuous outcomes

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 standard deviations (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 P values, t-values, CIs or standard errors (SEs), where reported in articles (Deeks 1997).

Where the vast majority of actual SDs are available and only a minority of SDs are unavailable or unobtainable, we will estimate them based on a prediction from a hierarchical model for SDs from those studies that did report them. Here we assume that any missing SD is exchangeable (i.e. broadly similar) with the reported SDs. We will also undertake a sensitivity analysis to examine the effect of the decision to use imputed data.

Where additional figures are not available or obtainable, and it is not deemed appropriate to use the Furukawa method described

above, the study data will not be included in the comparison of interest.

Assessment of heterogeneity

Pairwise meta-analyses

We will assess clinical heterogeneity by looking for obvious differences between participants, interventions and outcomes.

Assessment of transitivity across treatment comparisons

The assumption of transitivity (also known as consistency) is integral to network meta-analysis (NMA). Transitivity suggests that intervention A is comparable when in studies comparing A versus B, and A versus C. Transitivity can be assessed by examining the distribution of potential effect modifiers across comparisons in the network.

To evaluate the assumption of transitivity, we will extract study level characteristics considered to be potential effect modifiers (see above, baseline symptom severity, gender, participant age, duration of treatment, length of follow-up, proportion of participants with comorbidities, and year of trial publication), and examine their similarity visually using cross tabulations.

Assessment of reporting biases

For pairwise comparisons that include 10 or more studies, we will visually examine funnel plots for signs of reporting bias and small-study effects.

Data synthesis

All analyses will be undertaken in a Bayesian framework using OpenBUGS (www.openbugs.net), freely available software. Prior distributions will be reported. We will assess convergence based on two chains using the Brooks-Gelman-Rubin diagnostic plots and visually using history plots available in OpenBUGS. The number of iterations run as 'burn-ins' pre-convergence and the subsequent iterations will be reported.

Methods for indirect and mixed comparisons

We will conduct a NMA in order to simultaneously compare the interventions. In its simplest form a NMA is a combination of direct and indirect estimates of relative treatment effects in one single analysis. An indirect comparison enables the estimation of the effect of treatment B relative to treatment A via a common comparator C by statistically combining the summary effects from 'A versus C' and 'B versus C' studies ([Caldwell 2005](#); [Glenny 2005](#)). Through the combination of direct and indirect evidence

across a network of studies, a NMA can make inferences regarding the relative effectiveness of multiple interventions.

Given the nature of the included interventions, we expect some clinical heterogeneity between studies and therefore plan to use a random-effects model for all analyses. We will examine a fixed-effect model as a sensitivity analysis. For analysis at the intervention-level, a random-effects NMA will be conducted, taking into account the correlations induced by multi-arm trials ([Dias 2010](#); [Lu 2004](#)). For each comparison, the posterior mean effect estimate along with its 95% credible interval (CrI) will be reported. For the component level analysis, we will use the meta-regression models developed by [Welton 2009b](#) and will evaluate four models: a single-effect model (akin to standard meta-analysis), an additive main-effects model, a 2-way interaction model (allowing pairs of components to have either a bigger or smaller effect than would be expected from the sum of their effects alone) and a full-interaction model. We will fit models to different degrees of detail in the definitions of the components, data allowing and we will compare the model fit.

In addition to producing relative treatment effects for each comparison, NMAs allow an estimate of the relative ranking of interventions. We will rank interventions using a mean rank.

Methods for direct treatment comparisons

At the intervention-level, we will perform random-effects pairwise meta-analyses for each direct comparison for which there are two, or more, trials. The method of estimation for the pairwise analyses will be identical to the NMA, except we do not apply the consistency assumption, such that we obtain separate intervention-effect estimates for each pairwise comparison. We also assume that the heterogeneity parameter is common across intervention comparisons.

Subgroup analysis and investigation of heterogeneity

For each pairwise, direct comparison we will report τ^2 , the between-trial variability in treatment effects (heterogeneity) and the I^2 .

NMA assumes that the network has consistency, or that direct and indirect evidence are in agreement. However, this assumption can be violated either in the entire network or in certain parts of the network (i.e. loops of evidence) ([Bucher 1997](#)). To evaluate consistency, we will employ three strategies at the level of the treatment.

Model fit will be measured using the posterior mean of the residual deviance, which is a measure of the magnitude of the difference between the observed data and the model predictions for those data. Smaller values are preferred, and in a well-fitting model the posterior mean residual deviance should be close to the number of data points. We will also report the effective number of parameters, pD and Deviance Information Criteria (DIC), which

penalises model fit with model complexity. In comparing models, differences of ≥ 5 points for posterior mean residual deviance and DIC will be considered meaningful, with lower values being favoured (Welton 2009b). As a global check of consistency, we will compare the fit of a NMA model assuming consistency with a model that allows for inconsistency (also known as an unrelated treatment-effect model) (Dias 2013). If the inconsistency model has the smaller posterior mean residual deviance, heterogeneity, or DIC value, then this may indicate potential inconsistency in the data. If evidence of inconsistency is identified, then we will explore this further using node-splitting methods, where the direct and indirect estimates for a particular contrast are estimated separately (effectively relaxing the consistency assumption for a particular contrast) and then compared to form a node-split P value. We will use the above strategy, together with an evaluation of between-study heterogeneity, in our assessment of consistency.

Sensitivity analysis

Sensitivity analyses will be conducted, excluding studies at high risk or unclear risk of bias on the allocation concealment and blinding domains of Cochrane's 'Risk of bias' assessment tool. Additional sensitivity analyses include:

1. fixed-effect analyses for the pairwise and network meta-analyses will be run;
2. trials where missing data were imputed will be removed;
3. trials that use a non-operationalised diagnostic criteria will be removed;
4. waiting list will be removed from the network.

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* Indicates the major publication for the study

APPENDICES

Appendix I. OVID Medline: CCMD's core search strategy used to inform the specialised register

Description of the Specialised Register of the Cochrane Common Mental Disorders Group (CCMD-CTR)

The Cochrane Common Mental Disorders Group maintained a specialised register of randomized controlled trials at the University of Bristol to June 2016. This register contains over 40,000 reference records (primary and secondary reports of RCTs) for anxiety disorders, depression, bipolar disorder, eating disorders, self-harm and other common mental disorders which fall within the scope of the CCMD Group. The CCMD-CTR is a partially studies based register with 50% of the reference records tagged to c12,500 individually PICO coded study records. Reports of trials for inclusion in the register were collated from (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 were also sourced from international trial registries, drug companies, the hand-searching of key journals, conference proceedings and other (non-Cochrane) systematic reviews and meta-analyses. Details of CCMD's core (generic) search strategies (used to identify RCTs) can be found on the Group's website (<http://cmd.cochrane.org/>). By way of example, the MEDLINE search (used to inform the CCMD-CTR) is displayed below.

[N.B. In July 2016 the Cochrane Common Mental Disorders Group moved to the University of York.]

CCMD Core MEDLINE Search (a weekly Ovid search alert based on population and RCT filter only)

1. [MeSH Subject Headings]:

eating disorders/ or anorexia nervosa/ or binge-eating disorder/ or bulimia nervosa/ or female athlete triad syndrome/ or pica/ or hyperphagia/ or bulimia/ or self-injurious behavior/ or self mutilation/ or suicide/ or suicidal ideation/ or suicide, attempted/ or mood disorders/ or affective disorders, psychotic/ or bipolar disorder/ or cyclothymic disorder/ or depressive disorder/ or depression, postpartum/ or depressive disorder, major/ or depressive disorder, treatment-resistant/ or dysthymic disorder/ or seasonal affective disorder/ or neurotic disorders/ or depression/ or adjustment disorders/ or exp antidepressive agents/ or anxiety disorders/ or agoraphobia/ or neurocirculatory asthenia/ or obsessive-compulsive disorder/ or obsessive hoarding/ or panic disorder/ or phobic disorders/ or stress disorders, traumatic/ or combat disorders/ or stress disorders, post-traumatic/ or stress disorders, traumatic, acute/ or anxiety/ or anxiety, castration/ or koro/ or anxiety, separation/ or panic/ or exp anti-anxiety agents/ or somatoform disorders/ or body dysmorphic disorders/ or conversion disorder/ or hypochondriasis/ or neurasthenia/ or hysteria/ or munchausen syndrome by proxy/ or munchausen syndrome/ or fatigue syndrome, chronic/ or obsessive behavior/ or compulsive behavior/ or behavior, addictive/ or impulse control disorders/ or firesetting behavior/ or gambling/ or trichotillomania/ or stress, psychological/ or burnout, professional/ or sexual dysfunctions, psychological/ or vaginismus/ or Anhedonia/ or Affective Symptoms/ or *Mental Disorders/

2. [Keywords]:

eating disorder* or anorexia nervosa or bulimi* or binge eat* or (self adj (injur* or mutilat*)) or suicide* or suicidal or

parasuicid* or mood disorder* or affective disorder* or bipolar i or bipolar ii or (bipolar and (affective or disorder*)) or mania or manic or cyclothymic* or depression or depressive or dysthymi* or neurotic or neurosis or adjustment disorder* or antidepress* or anxiety disorder* or agoraphobia or obsess* or compulsi* or panic or phobi* or ptsd or posttrauma* or post trauma* or combat or somatoform or somati#ation or medical* unexplained or body dysmorphi* or conversion disorder or hypochondria* or neurastheni* or hysteria or munchausen or chronic fatigue* or gambling or trichotillomania or vaginismus or anhedoni* or affective symptoms or mental disorder* or mental health).ti,kf.

3. [RCT filter]:

(controlled clinical trial.pt. or randomized controlled trial.pt. or (randomi#ed or randomi#ation).ab,ti. or randomly.ab. or (random* adj3 (administ* or allocat* or assign* or class* or control* or determine* or divide* or distribut* or expose* or fashion or number* or place* or recruit* or substitut* or treat*)).ab. or placebo*.ab,ti. or drug therapy.fs. or trial.ab,ti. or groups.ab. or (control* adj3 (trial* or study or studies)).ab,ti. or ((singl* or doubl* or tripl* or trebl*) adj3 (blind* or mask* or dummy*)).mp. or clinical trial, phase ii/ or clinical trial, phase iii/ or clinical trial, phase iv/ or randomized controlled trial/ or pragmatic clinical trial/ or (quasi adj (experimental or random*)).ti,ab. or ((waitlist* or wait* list* or treatment as usual or TAU) adj3 (control or group)).ab.)

4. (1 and 2 and 3)

[Field Tags: ti-title; ab-abstract; kf-keyword heading word]

Records were screened for reports of RCTs within the scope of CCMD. Primary and secondary reports of RCTs were tagged to the appropriate study record. Similar weekly search alerts were also conducted on OVID EMBASE and PsycINFO, using relevant subject headings (controlled vocabularies) and search syntax, appropriate to each resource.

Appendix 2. Search strategies

Search 1: Psychological therapies for depression A broad search of all psychological therapies for depression, for the HIRED-MAP project (High Impact Reviews of Effectiveness in Depression - Meta-analysis of Psychological Therapies).

1a. CCMDCTR-Studies (all years to 1-January-2012, updated 10-April-2014)

#1 (depress* or dysthymi*):sco and (*therap* or train*):sin

[Search fields: sco:health care condition; sin:intervention]

1b. CCMDCTR-References (all years to 1-January-2012, updated 10-April-2014)

#1 (therap* or psychotherap*):ti,ab

#2 (psychotherapy):kw,ky,mh,emt

#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) [all fields]

#4 (abreaction or “acting out” or “age regression” or ((assertive* 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 biofeedback or catharsis or cognitive or “mind training” or counsel* or “contingency management” or countertransference or “covert sensitization” or “eye movement desensiti*” or “crisis intervention” or “dream analysis” or “emotional freedom” or “free association” or “functional analys*” or griefwork or “guided imagery” or hypno* or imagery or meditation* or “mental healing” or mindfulness* or psychoanaly* or psychodrama or psychoeducat* or “psychological support*” or “psychosocial support*” or “social support*” or “family support*” or psychotherap* or relaxation or “role play*” or “self analysis” or “self esteem” or “sensitivity training” or (support* and group*) or therapist or “therapeutic technique*” or “transactional analysis”) [all fields]

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

#6. (depress* or dysthymi*):ti,ab

#7. Tagged to CCMDCTR-Study=empty

[Search fields: ti:title; ab:abstract; kw:Cochrane Review Group (CRG) keywords; ky: other keywords; emt: EMTREE headings; mh: MeSH headings]

Search 2: Cognitive behavioural therapies versus treatment as usual for depression

A cross-search of CCMD-CTR-Studies and CCMD-CTR-References Registers. (10-Apr-2014 to 7-Aug-2015, updated 6-June-2016)

[N.B. Prior to this date, studies were identified from the global HIRED-MAP searches, detailed above]

#1. ((cognitive NEAR2 (behavi* or modif* or restructur* or intervention or treatment* or *therap* or train*))) [all fields]

#2. cognitive:ti

#3. (*CBT* or cognitive-behavi*) [all fields]

#4. (RET OR PST):ab

#5. (problem-sol* or "problem sol*" or psychoeducat* or psycho-educat* or psychodrama or psycho-drama* or "rational emotive" or "reality *therap*" or "role play*" or schema or schemas or schemata)

#6. (self-control or (self* NEAR2 (control or efficacy))) [all fields]

#7. "stress manage*" [all fields]

#8. (group NEXT (*therap* or program* or treatment))[all fields]

#9. (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8)

#10. depress*:ti

#11. (depression or depressive):kw,ky,mh,emt

#12. (depress* and (Beck* or BDI* or DSM* or "Diagnostic and Statistical Manual of Mental Disorders" or Hamilton or HAM-D or HAMD or "International Classification of Diseases" or ICD-10)):ab

#13. (MDD or (depress* NEAR2 (diagnos* or episode* or disorder or major or scale* or score* or unipolar))):ab

#14. (#10 or #11 or #12 or #13)

#15. (#9 and #14)

#16. (treatment-as-usual or (treatment* NEAR2 usual) or (standard NEAR2 care) or (routine NEAR2 care) or (usual NEAR2 medication*) or (usual NEAR2 care) or TAU):ti,ab

#17. (waitlist* or wait-list* or waiting-list* or "wait* list*" or (waiting next (condition or control)) or WLC):ti,ab

#18. ("delayed treatment*" or "no treatment*" or "non treatment*" or nontreatment* or "minim* treatment*" or "untreated group*" or "untreated control*" or "without any treatment"):ti,ab

#19. (untreated NEAR3 (patients or participants or subjects or group* or control*)):ti,ab

#20. ("no intervention*" or non intervention* or non-intervention* or without any intervention*):ti,ab

#21. ("receiv* nothing" or "standard control"):ti,ab

#22. ("no therap*" or "non therap*" or nontherap* or "minim* therap*" or "no contact" or pseudotherap* or "therap* as usual" or "usual therap*"):ti,ab

#23. ("reference group" or "observation group"):ti,ab

#24. ("convention* treatment" or "conventional *therap*" or "standard treatment*"):ti,ab

#25. (#16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24)

#26. (#15 and #25)

Search 3: Multimedia-delivered cognitive behavioural therapy versus face-to-face cognitive behavioural therapy for depression in adults (All years to 10-June-2016)

A cross-search of CCMD-CTR-Studies and CCMD-CTR-References Registers.

#1 ("chat room*" or distance* or etherap* or e-therap* or "instant messag*" or iCBT* or i-CBT or cCBT or c-CBT or internet* or web* or www* or online* or on-line* or mHealth or multimedia* or multi-media* or mobile or email* or e-mail* or remote or texting or "text message" or SMS or telehealth* or telemed* or telepsych* or teletherap* or tele-therap*) [all fields]

#2 (android or app or apps or cellphone* or "cell phone*" or "digital device*" or "digital technolog*" or iphone* or i-phone* or ipad* or i-pad* or "mobile phone" or smartphone or "smart phone") [all fields]

#3 (MoodGym* or "Mood Gym" or "Beat* the Blues") [all fields]

#4 (computer* near (*CBT* or cognitive)):ti,ab

#5 (ecompared or e-compared) [all fields]

#6 (blended or bCBT) [all fields]

#7 (DVD or CD-ROM or CDRom) [all fields]

#8 ((manual or book or booklet or leaflet or pamphlet) and (*face* or therapist* or psychotherap*))

#9 (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8)

#10 (depress* or mood or dysthymi* or "affective disorder*" or "affective symptom*"):ti,ab,kw,ky,mh,mc,emt

#11 (#9 and #10)

#12 telephone [all fields]

#13 #12 and #10

#14 #11 or #14

Search 4: 'Third wave' cognitive and behavioural therapies versus treatment as usual for depression

(1-Feb-2013, updated 9-July-2015 and 6-June-2016)

[N.B. Prior to this date, studies were identified from the global HIRED-MAP searches, detailed above]

A cross-search of CCMD-CTR-Studies and References Register

#1 depress*:ti,ab,kw,ky,mh,mc,emt

#2 (mindfulness* or "third wave" or third-wave or (*therap* and (acceptance* or commitment*)) or experiential or (cognitive* and (restructur* or defusion)) or (behavio* and (activation or modification)) or (thought* and suppress*) or rumination) [All Fields]

#3 (#1 and #2)

CONTRIBUTIONS OF AUTHORS

NW, DSK, DMC, NJW and RC conceived the project and wrote the application for funding.

SRD drafted the initial protocol and data extraction forms, with input from DMC, JALL, SD, NJW, NW, DSK and RC. All authors have contributed to the protocol design and content, for example at team meetings and through formal protocol review at various times since the study was funded.

DMC, JALL and NJW contributed to the statistical methods.

SD developed the search strategies, screened abstracts and maintained the specialised register. All authors contributed to the study eligibility criteria, selection of subgroups, and the selection of outcomes and time-points.

RC, NW and DSK are responsible for the project oversight.

All authors have approved this version for publication

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