

COMAD: Comprehensive Meta-Aalysis for Depression

[PROTOCOL]

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Background

Unipolar major depression is the third leading cause of total disease burden and the largest source of non-fatal disease burden worldwide and is expected to show a rising trend over the next 20 years (WHO 2008). The recent WHO World Mental Health Survey revealed the average lifetime and 12-month prevalence estimates of DSM-IV major depressive episode of 14.6% and 5.5% in the ten high-income and 11.1% and 5.9% in the eight low- to middle-income countries that they surveyed (Bromet et al. 2011). Depression is not only associated with marked personal morbidity and dysfunction but also is responsible for substantial direct and indirect economic costs to the society (Luppa et al. 2007).

The most common and recommended treatment options for major depression are pharmacological and psychological interventions (NICE 2009; American Psychiatric Association 2010). Both modalities have substantive evidence to support their general effectiveness (Turner et al. 2008; Driessen et al. 2010; Lynch et al. 2010; Gibbons et al. 2012). The prescribing of antidepressants has increased dramatically in many Western countries over the last 20 years, mainly with the advent of selective serotonin reuptake inhibitors and other newer agents, and they remain the mainstay of treatment for depression in health care settings (Gartlehner et al. 2011). However, many (Churchill et al. 2000; van Schaik et al. 2004; Riedel-Heller et al. 2005) if not all (Dobscha et al. 2007) surveys attest to the patients' preference for psychological therapies over that by antidepressants. Psychological therapies therefore provide an important alternative intervention for depressive disorders. For either of these treatment modalities, however, adherence remains less than optimal (Oei and Kazmierczak 1997; Vergouwen et al. 2003; van Geffen et al. 2009).

Which then is more efficacious and acceptable in the acute phase treatment of major depression, psychotherapies or drug therapies? And of the various available options within these two broad groups of interventions, is there any particular drug or psychotherapy that stands out and is clinically superior to the others? Given the pragmatic importance of this and related clinical questions, it is no surprise that several important systematic reviews and meta-analyses have already been conducted and reported in the literature. Some are clearly outdated (Dobson 1989; Gloaguen et al. 1998; DeRubeis et al. 1999). Some compared antidepressant medications and psychotherapies for depression without further differentiation and may have overlooked important differences between and among these two broad groups of interventions (Imel et al. 2008), while others focused on one psychotherapeutic approach only, most often CBT (Butler et al. 2006). Still others have essayed to differentially evaluate different psychotherapies either as subgroup analyses (Cuijpers et al. 2008) or each separately (Hollon and Ponniah 2010) but still treated all antidepressants as a single treatment modality.

When a range of interventions are available for the same disorder, of which some are compared against others in randomised trials, indicating possible yet no definitive superiority or inferiority of one over the other, a new meta-analysis approach may be of particular value in making all comparisons through the optimum use of the available evidence. Multiple-treatments meta-analysis (MTM, also known as network meta-analysis) is a statistical technique that allows both direct and indirect comparisons to be undertaken, even when two of the treatments have not been directly compared (Higgins and Whitehead 1996; Lumley 2002). In other words, it is a generalisation of standard pair-wise meta-analysis for A vs B trials, to data structures that include, for example, A vs B, B vs C, and A vs C trials.

MTM can summarise RCTs of several different treatments providing point estimates (together with 95% credibility intervals [CIs]) for their association with a given endpoint, as well as an estimate of incoherence (that is, a measure of how well the entire network fits together, with small values suggesting better internal agreement of the model). MTM has already been used successfully in psychiatry (Cipriani et al. 2009) and in other fields of medicine (Psaty et al. 2003; Stettler et al. 2007). Two fruitful roles for MTM have been identified (Lu and Ades 2004):

- (i) to strengthen inferences concerning the relative efficacy of two treatments, by including both direct and indirect comparisons to increase precision and combine both direct and indirect evidence;
- (ii) to facilitate simultaneous inference regarding all treatments in order for example to select the best treatment.

Considering how important comparative efficacy could be for clinical practice and policy making, it is important to use all the available evidence to estimate potential differences in efficacy among available treatments. MTM thus offers the best use of currently available evidence to arrive at the most informative inference regarding which of the many available treatments work better than the others. Consumers of health care research, namely patients and their families, clinicians, and policy makers, have been in dire need of such

comparative effectiveness research in the acute phase treatment of major depression. We have thus far conducted MTMs for drug therapies for depression (Cipriani et al, in preparation) and those for psychotherapies depression (Churchill et al, in preparation) separately, and the present MTM essays to combine the two in order to elucidate the relative efficacy and acceptability of various available options in pharmacotherapy and psychotherapy in major depression.

Objectives

To compare the efficacy and acceptability of different psychotherapies, drug therapies and their control conditions in the acute phase treatment of major depression in adults

Methods

Criteria for considering studies for this review

Types of studies

Inclusion criteria

Randomised controlled trials (RCTs) comparing one against another of the drugs or psychotherapies in question (see the list below) or against pill placebo or other control conditions as monotherapy in the acute phase treatment of major depression will be included. Studies in which two treatments are compared and in which a co-intervention (except for protocolized antidepressant treatment intended as combination treatment) is simultaneously provided will be accepted as a comparison of the two treatments when the co-intervention is equally administered in both arms. We will accept open studies and studies in which outcome assessors were not blinded to the treatments (Wood et al. 2008). The influence of including open studies will be assessed in a sensitivity analysis.

For trials which have a crossover design only results from the first randomisation period will be considered. Cluster-randomised trials will be included only if intra-cluster correlation coefficients are reported.

Exclusion criteria

Quasi-randomised controlled trials, in which treatment assignment is decided through methods such as alternate days of the week, will be excluded.

Types of participants

Participant characteristics

Inclusion criteria

Patients between ages 18 and 75, of both sexes with a primary diagnosis of unipolar major depression, diagnosed according to any of the following operationalised criteria: Feighner criteria, Research Diagnostic Criteria, DSM-III, DSM-III-R, DSMIV or ICD-10. Operationalised criteria essentially resembling these official ones will also be eligible.

Exclusion criteria

Studies that used non-operationalised diagnostic criteria or relied on a clinician or self-report depression scale to identify depression caseness will be excluded.

Differences in cognitive capabilities and physiologies among younger or elderly people influence the effectiveness and acceptability of psychotherapies and pharmacotherapies (Pinquart et al. 2006). Therefore studies of children and adolescents aged ≤ 18 or of older people where the mean age of participants was ≥ 75 years will be excluded.

Trials that focused on treatment-resistant or chronic depression including dysthymia will be excluded, because we are interested in the treatment options for the acute phase treatment. Similarly, studies of interventions designed to prevent a future episode of depression will be excluded. Trials in which greater than 20% of the participants suffered from bipolar depression will also be excluded.

Trials that focused on depression among participants who all had a concurrent primary diagnosis of another Axis I or II disorder will be excluded. Existence of concurrent secondary diagnosis of another psychiatric disorder is allowed.

Trials that focused on depression among patients with a certain concomitant medical illness will be excluded. RCTs of women with post-partum depression will also be excluded, because post-partum depression appears

to be clinically different from major depression (Cooper and Murray 1998).

Setting

Inclusion criteria

Studies conducted in primary care and community-based settings or in outpatient specialist settings are eligible. We will include studies with volunteer participants as well as those recruited from referrals. Studies that focused on specific populations (eg depressed participants at a specific work place, depressed care givers, etc) will be included if the participants all met the criteria for major depression.

Exclusion criteria

Studies conducted in inpatient settings will be excluded from the review, as psychotherapies require voluntary participation from the patients, which may not always be guaranteed in inpatient settings.

Types of interventions

Included interventions

We will include the following 10 psychotherapies, 18 antidepressant drugs as well as five control conditions in our systematic reviews.

Psychological interventions

The psychological therapy intervention was required to be delivered through face to face meetings between the patient and therapist. Interventions in which face to face therapy was augmented by telephone or internet-based support were included in the review. Psychological therapy approaches conducted on either an individual or on a group basis were also included.

In order to use the common time frame with acute phase drug treatments, the duration of the psychological intervention had to be between 4 and 16 weeks.

A diverse range of psychological therapies is now available for the treatment of depression. In our previous MTM of psychotherapies for depression (Churchill et al, in preparation), we categorized psychological therapies broadly into four separate philosophical and theoretical schools, each of which contains a number of differing and overlapping psychotherapeutic approaches. They are psychoanalytic/dynamic (Freud 1900; Jung 1921; Klein 1932), humanistic (Maslow 1943; Rogers 1951), behavioural (Watson 1924; Skinner 1953; Marks 1981), and cognitive approaches (Beck et al. 1979; Ellis 1979). Beck and Ellis have both acknowledged the value of behavioural therapy, and during the 1980s and 1990s, the last two approaches merged to form cognitive behavioural therapy (CBT) (Roth and Pilling 2008). Some other psychotherapeutic approaches, such as interpersonal therapy (Klerman et al. 1984), also explicitly integrate components from several theoretical schools. Based on our previous MTM, we will focus the current MTM on the following psychotherapies which showed promises and /or provided well-delineated reproducible procedures.

Behaviour therapies

1. Behavioural therapy (Lewinsohn)

Lewinsohn 1974 proposed that depressed individuals have low rates of pleasant activities and obtained pleasure, that their mood covaries with rates of pleasant and aversive activities, that their mood improves with increases in pleasant activities, and that they lack social skills during the depressed phase. Therefore, behavioural therapy based on the approach developed by Lewinsohn and colleagues involves helping individuals increase their frequency and quality of pleasant activities, producing corresponding improvement in mood and overall quality of life (Lewinsohn 1974).

2. Social skills training/assertiveness training

The social skills training model (SST) proposes that depressed people may have difficulty initiating, maintaining and ending conversations (Jackson 1985). Because of these deficits, the individual is unable to elicit mutually reinforcing behaviour from other people in their environment. SST subsumes assertion and conversational skills, together with more specialised subskills such as dating and job interview skills. Four social contexts of interacting with strangers, friends, family members and people at work or school are targeted (Bellack 1980) and interventions such as instruction, modelling, rehearsal, feedback and reinforcement are used to enable the development of new responses (Jackson 1985). As assertiveness training comprises a key component of SST, it will be included in the SST category.

Cognitive-behaviour therapies

3. Cognitive therapy

The cognitive model of depression (Beck 1979) proposes that biased thinking and unrealistic cognitive appraisals of events negatively affect feelings and behaviour in a reciprocal interaction. Negative automatic thoughts are thought to be influenced by schema, or thought patterns, which are formed early in life. These are characterised in depressed individuals as a negative cognitive triad, in which views of the self, world and future are affected. CT aims to restructure the individual's unhelpful appraisal of life events, through understanding the relationship between thoughts, feelings and behaviours, recognising and monitoring negative automatic thoughts, and enabling the development of more realistic and balanced appraisals. Studies of interventions described as 'CBT' by trial authors, but which are based predominantly on cognitive restructuring methods, and/or cite the Beck 1979 manual, will be included in this group.

4. Problem-solving therapy

PST was developed as an intervention to train individuals to function as their own therapist (D'Zurilla 1971). Five overlapping stages are proposed to represent the problem-solving process, including general orientation, problem definition and formulation, generation of alternatives, decision-making and verification. Training in problem-solving involves teaching individuals these skills and providing guidance in their application for identified problems (Dobson 2001). As a pragmatic and flexible approach, PST has been adapted and manualised for evaluation in a number of different populations, including depression (Nezu 1986).

5. Coping with Depression course

Developed and evaluated as a group intervention for depression (Lewinsohn 1984), the CWD course for adults is a structured, psychoeducational programme that emphasises learning simple behavioural principles such as activity monitoring, scheduling and progressive goal achievement. Participants learn to improve social skills, use relaxation techniques, increase or rediscover involvement in pleasant activities and to use simple cognitive strategies.

3rd wave therapies

6. Acceptance and commitment therapy

In acceptance and commitment therapy (ACT) (Hayes 1999; Hayes 2004) therapists aim to transform the relationship between the experience of symptoms and difficult thoughts/feelings, so that symptoms no longer need to be avoided and become just uncomfortable transient psychological events (Harris 2006). In this way, symptom reduction becomes a by-product of treatment (Harris 2006). Clients are encouraged to develop psychological flexibility through six core principles: cognitive defusion (perceiving thoughts, images, emotions, and memories as what they are, rather than what they appear to be); acceptance (allowing these to come and go without struggling with them); contact with the present moment (awareness of and receptiveness to the here and now); use of the observing self (accessing a transcendent sense of self); personal values (discovering what is most important to one's true self); and committed action (setting goals according to values and carrying them out responsibly) (Hayes 1999). In terms of committed action, ACT uses methods in line with traditional behaviour therapy, such as exposure, skills acquisition and goal setting.

7. Extended behavioural activation

The original behavioural activation (BA) approach manualised by Jacobson 1996 includes teaching relaxation skills, increasing pleasant events and social and problem-solving skills training, and is regarded as a traditional behavioural therapy model. More recently, the BA approach has been extended by Martell 2001, building on the original behavioural models of depression (Lewinsohn 1974) by introducing a contextual approach to depression. The extended BA model suggests that just as avoidance maintains anxiety, avoidant coping patterns (withdrawal from situations and people) maintain depressed mood, and, therefore, avoidant coping is targeted as a primary problem. Following functional analysis, in which a detailed assessment of how an individual maintains depressive behaviour is carried out, the individual is taught to formulate and accomplish behavioural goals, irrespective of prevailing negative thoughts and mood states (Hopko 2003). Traditional behavioural therapy strategies such as activity charts, relaxation training and increasing pleasant events are also used (Dobson 2001). A second BA approach, behavioral activation treatment for depression (BATD) (Lejuez 2001), proposes that depression is maintained through the use of reinforcers such as increased social attention and escape from aversive tasks. Following functional analysis as described in the extended BA model above, access is weakened to reinforcements such as sympathy and escape from responsibility, and

healthy behaviour is systematically activated through the use of goal setting and increased activities (Hopko 2003).

8. Psychodynamic therapies

9. Interpersonal therapy (IPT)

IPT was developed in order to operationalise what was considered to be a set of helpful procedures commonly used in psychotherapy for depressed outpatients (Weissman 2007) for a series of treatment studies in depression conducted in the US (Elkin 1989; Frank 1990). Whilst described by the International Society for Interpersonal Psychotherapy (ISIPT) as having 'no specific theoretical origin' (isIPT [ND]), IPT draws in part from attachment theory (Bowlby 1980), and is based on the premise that depressive symptoms may be influenced strongly by the disruption of close personal attachments in four key domains of grief, role disputes, role transitions and interpersonal deficits (Weissman 2007). Within the therapeutic process, IPT uses techniques borrowed from other therapies such as cognitive-behaviour therapy and brief crisis intervention (isIPT [ND]), including clarification (seeking to obviate the patient's biases in describing interpersonal issues), role playing and communication analysis, together with supportive listening, encouragement of affect and use of the therapeutic relationship. Since the development of IPT in 1984, there has been ongoing debate over its potential categorisation as a time-limited psychodynamic psychotherapy (Markowitz 1998). Systematic reviews of psychodynamic therapy approaches for depression have obtained different findings according to its inclusion (Crits 1992; Anderson 1995) or exclusion (Svartberg 1991; Leichsenring 2004). Following detailed comparison of IPT and brief psychodynamic psychotherapy, Markowitz 1998 has concluded that despite overlaps and similarities, IPT is distinct from STPP. Given its use of CBT techniques, coupled with its psychodynamic features and atheoretical origins, IPT will be considered an integrative therapy for the purposes of this review, in accordance with technical integration principles.

10. Non-directive/supportive therapies

In person-centred therapy (PCT), core conditions of empathy, genuineness and unconditional positive regard, considered to be the 'antithesis' of a therapeutic technique (Cooper 2008) are considered sufficient to facilitate personality change (Rogers 1951). Use of a non-directive stance by the therapist is a key feature of PCT (Mearns 2007). Moving through three phases of trust, intimacy and mutuality within the therapeutic relationship (Mearns 2007), change occurs as the client shifts from a negative evaluation of self towards a belief that they are worth caring for (Thorne 2002). Therapies described as 'non-directive' or 'supportive', and not explicitly underpinned by person-centered theory, principles and supporting references, will be included here also.

Antidepressant drugs

We will include the following selected first- and second-generation antidepressants.

1. TCA

Amitriptyline, Clomipramine

2. SSRI

Citalopram, Escitalopram, Fluoxetine, Fluvoxamine, Paroxetine, Sertraline

3. SNRI

Desvenlafaxine, Duloxetine, Milnacipran, Venlafaxine

4. Other second-generation antidepressants

Agomelatine, Bupropion, Mirtazapine, Reboxetine, Trazodone, Vilazdone

We will include only studies randomising patients to drugs within the therapeutic dose (Cipriani et al. 2011). Both fixed-dose and flexible-dose designs will be accepted.

Control comparators

Control comparators will be categorised as follows. In each study, descriptions of the various control conditions will be scrutinised to ensure that they did not comprise an active psychological therapy treatment.

1. Treatment as usual (TAU)

In this condition, participants could 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. Standard care, usual care or no treatment conditions were also included in this category.

2. Waiting list (WL)

A commonly used 'treatment as usual' is to randomise participants to active intervention groups and control group, to provide the active intervention to both groups but to delay delivery of the intervention to the control group until after those in the intervention group have completed treatment. As in TAU, patients in the WL condition could receive any appropriate medical care during the course of the study on a naturalistic basis.

3. Attention placebo (AP)

This was defined as a control condition that is regarded as inactive both by researchers and by participants in a trial

4. Psychological placebo (PP)

This was defined as a control condition that is regarded as inactive by researchers in a trial but is regarded as active by the participants

We planned to document additional naturalistic treatment(s) received by participants in both the control and active comparisons for each included study.

5. Pill placebo

Excluded interventions

Psychological therapy models based on social constructionist principles (that focus on the ways in which individuals and groups participate in the construction of their perceived social reality) including couples therapy (Barbato 2006), family therapy (Henken 2007), solution-focused therapy, narrative therapy, personal construct therapy, neuro-linguistic programming and brief problem-solving (Watzlavick 1974) will be excluded. These psychological therapies work with patterns and dynamics of relating within and between family, social and cultural systems in order to create a socially constructed framework of ideas (O'Connell 2007), rather than focusing on one individual's reality.

Guided self-help, in which the practitioner provides brief face-to-face non-therapeutic support to patients who are using a self-help psychological therapy intervention, were excluded, as were bibliotherapy and writing therapies.

Psychological therapies provided wholly by telephone or over the internet were also excluded.

Studies of dual modality treatments, in which patients are randomised to receive a psychological therapy intervention combined with pharmacological treatment, were excluded from the current review.

Component or dismantling studies (in which the effectiveness of individual components of a cognitive-behavioural therapeutic approach are investigated) will not be included unless there were viable comparisons to be made with another psychological therapy approach.

Outcome measures

Primary outcomes

(1) Treatment efficacy: the number of patients who respond to treatment, based on changes on Hamilton Rating Scale for Depression (HAM-D) (Hamilton 1960) or Montgomery-Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg 1979) or Beck Depression Inventory (Beck et al. 1961), or any other validated depression scale at the end of acute phase treatment (8 weeks, range 4-16 weeks). Many studies define response by 50% or greater reduction on the rating scale but some studies define response using Jacobson's Reliable Change Index (Jacobson and Truax 1991). We will focus on 50% or greater reduction in depression severity. If the original authors report several outcomes corresponding with our definition of response, we will give preference to HAM-D. Any version of HAM-D will be accepted.

(2) Treatment acceptability: the number of participants who drop out of treatment for any reasons during the first 8 weeks of treatment (range: 4-16 weeks).

Secondary outcomes

(3) Remission: The number of patients who remit on treatment, based on the endpoint absolute status of the patients, as measured by HAM-D, MADRS, or any other validated depression scale. Examples of definitions of remission include 7 or less on 17-item HAM-D (Furukawa et al. 2007) or 11 or less on MADRS (Bandelow et al. 2006); 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 HAM-D.

(4) Severity of depression symptoms, based on a continuous outcome of group mean scores at the end of treatment using HAM-D, MADRS, BDI, or any other validated depression scale.

Search methods for identification of studies

Electronic searches

1. CCDANCTR Specialised Registers

We will search two clinical trials registers created and maintained by the Cochrane Depression, Anxiety and Neurosis Group (CCDAN), the CCDANCTR-Studies Register and the CCDANCTR-References Register. References to trials for inclusion in the Group's registers are collated from routine (weekly) searches of MEDLINE, EMBASE and PsycINFO, quarterly searches of the Cochrane Central Register of Controlled Trials (CENTRAL) and additional ad hoc searches of other databases (PSYINDEX, LILACS, AMED, CINAHL). These searches employ generic terms for depression, anxiety and neuroses; together with sensitive (database specific) RCT filters. Details of the generic search strategies can be found in the 'Specialized Register' section of the Cochrane Depression, Anxiety and Neurosis Group's module text.

References to trials are also sourced from international trials registers via the World Health Organisation's trials portal (<http://apps.who.int/trialsearch/>); drug companies; the hand-searching of key journals, conference proceedings and other (non-Cochrane) systematic reviews and meta-analyses. Trial databases of the following drug-approving agencies (the Food and Drug Administration in the USA, the Medicines and Healthcare products Regulatory Agency in the UK, the European Medicines Agency in the EU, the Medicines Evaluation Board in the Netherlands, the Medical Products Agency in Sweden, the Pharmaceuticals and Medical Devices Agency (PMDA) in Japan, the Therapeutic Goods Administration (TGA) in Australia) will be hand-searched for published, unpublished and ongoing controlled trials. The National Institute for Clinical Excellence (UK) and the Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Germany) will also be contacted for additional information. No language restriction will be applied.

The CCDANCTR-Studies Register

The CCDANCTR-Studies Register contains over 11,000 trials for the treatment or prevention of depression, anxiety and neurosis. Each trial has been coded using the EU-Psi coding manual (as a guide) and includes information on intervention, condition, comorbidities, age, treatment setting etc.

In order to identify all the studies that compared among the psychotherapies in question, the studies register will be searched using the following search terms:

Condition = (depress* or dysthymi*) and Intervention = (*therap* or training)

In order to identify all the studies that compared the psychotherapies in question against the included antidepressants, the studies register will be searched using the following search terms:

Condition=depress* AND Intervention = (cognitive* or behavi* or *therap* or training or treatment or counsel* or psycho* or humanistic or mindfulness) AND Intervention=(Amitriptylin* or Chlorimipramin* or Clomipramin* or Chlomipramin* or Clorimipramine or or Citalopram or Escitalopram or Fluoxetine or Fluvoxamine or Paroxetine or Sertraline or Desvenlafaxine or Duloxetine or Milnacipran or Venlafaxine or Agomelatine or Bupropion or Mirtazapine or Reboxetine or Trazodone or Vilazdone or tricyclic drugs" or (serotonin or selective) and "reuptake inhibitors"))

The CCDANCTR-References Register

The CCDANCTR-References Register contains bibliographic records of reports of trials coded in the CCDANCTR-Studies Register together with several other uncoded references (total number of records=24,500). This register will be searched using a comprehensive list of terms for 'psychotherapies' as indicated in below. Records already retrieved from the search of the CCDANCTR-Studies Register will be de-duplicated.

1:Title/Abstract=therap* or psychotherap*

2:Keywords=psychotherapy

3:Free-Text=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:Free-Text=(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 “psycho* support*” or psychotherap* or relaxation or “role play*” or “self analysis” or “self esteem” or “sensitivity training” or “support* group*” or therapist or “therapeutic technique*” or “transactional analysis”)

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

2. In order to identify all published and unpublished RCTs that compared one antidepressant with another or placebo in the treatment of major depression, all the original databases will be searched using the following phrase: [depress* or dysthymi* or adjustment disorder* or mood disorder* or affective disorder or affective symptoms] and combined with a list of all included antidepressants.

We are aware that there are many trials carried out in China (Chakrabarti et al. 2007). However, for many of these studies only incomplete or conflicting information is available and it has been reported many of them do not use appropriate randomisation procedures (Wu et al. 2006). In an effort to avoid the potential biases that may be introduced by including these trials without further information, we will exclude these studies.

Searching other resources

1. Reference lists

The references of all selected studies will be searched for more published reports and citations of unpublished studies. Relevant review papers will be checked.

2. Personal communication

Subject experts will be contacted to check that all relevant studies, either published or unpublished, have been considered for inclusion.

Data collection

Selection of studies

Two review authors will examine the titles and abstracts of all publications obtained through the search strategy. Full articles of all the studies identified by either of the review authors will then be obtained and inspected by the same two review authors to identify trials meeting the following criteria:

1. Randomised controlled trial;
2. Participants have depression diagnosed by operationalised criteria
3. And compared any of the above-listed psychotherapies or drug therapies

Conflicts of opinion regarding eligibility of a study will be discussed with a third review author, having retrieved the full paper and consulted the authors if necessary, until consensus is reached.

Data extraction and management

Data from each study will be extracted independently by two review authors. Any disagreement will be resolved through discussion and in consultation with the principal investigators. Where necessary, the authors of the studies will be contacted for further information.

Information relating to study population, sample size, interventions, comparators, potential biases in the conduct of the trial, and outcomes will be abstracted from the original reports into specially designed paper forms then entered into a spreadsheet.

Management of time points

It is a problem of systematic reviews that usually trials have different durations. Clinically, the assessment of efficacy after 8 weeks of treatment or after 24 weeks or more may lead to differences in terms of treatment outcome. Clinicians need to know whether (and to what extent) treatments work within a clinically reasonable period of time. Unfortunately, there is no consensus on what the appropriate duration of an acute phase trial is. In the present review, acute treatment will be defined as an 8-week treatment in both the efficacy and acceptability analyses. If 8-week data are not available, we will use data ranging between 4 to 16 weeks and the time point given in the original study as the study endpoint will be given the preference. Longer-term studies will be excluded if they do not provide data for the 4-16 weeks period.

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 (Higgins and Green 2011). The following 10 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 the primary outcome: was knowledge of the allocated treatment adequately prevented during the study?
4. Incomplete outcome data for the primary outcome: were incomplete outcome data adequately addressed?
5. Selective outcome reporting: are reports of the study free of suggestion of selective outcome reporting?

We also assessed

6. Researcher allegiance
 7. Therapist allegiance
 8. Therapist qualification
 9. Treatment fidelity
- in the case of psychotherapy interventions, and
10. Sponsorship

in the case of drug trials. We did not classify a study as industry-sponsored when only the medication was provided by the pharmaceutical company.

Other sources of bias included but are not limited to:

- Suboptimal randomization, such as recruiting additional patients to one arm which had a large number of dropouts, or reporting only a subset of the patients randomised without stratification (e.g. only those with major depression are reported when the authors originally randomised all patients who wanted to take the course)
- Stopped early due to some data-dependent process (including a formal-stopping rule)
- Had extreme baseline imbalance
- Differential treatment duration among the arms
- Insufficient delivery of treatment or insensitive scales to measure outcomes, leading to null results

A judgment on the risk of bias will be made for each domain, based on the following three categories:

High risk of bias

Low risk of bias

Unclear risk of bias.

Two independent review authors will assess the risk of bias in selected studies. Any disagreement will be resolved through discussion and in consultation with the principal investigators. Where necessary, the authors of the studies will be contacted for further information.

Statistical analyses

Measures of treatment effect

Considering that depression trials are usually small and that data distribution is difficult to assess for studies with small samples, in this review priority will be given to the use and analysis of dichotomous variables both for efficacy and acceptability.

Dichotomous outcomes: these outcomes will be analysed by calculating a pooled odds ratio (OR) and 95%

confidence intervals for each comparison.

Continuous outcomes: Where different measures are used to assess the same outcome, data will be pooled with standardised mean difference (SMD) and 95% confidence intervals calculated.

Dealing with missing data

Missing dichotomous data will be managed according to the intention to treat (ITT) principle, and it will be assumed that patients who dropped out after randomisation had a negative outcome. When dichotomous efficacy outcomes are not reported but baseline mean and endpoint mean and standard deviation of the depression rating scales are provided, we will calculate the number of responding patients at 8 weeks (range 4 to 16 weeks) employing a validated imputation method (Furukawa et al. 2005). We are aware that other methods to impute response rate are available and have been investigated (Anzures-Cabrera et al. 2011). Even though these imputation methods are valid and may give odds ratios (ORs) with narrower CIs, they only produce logORs and their variances rather than raw data. As we opt for a model based on 2x2 tables using the binomial likelihood, the Furukawa method will be used in our review.

Missing continuous data will either be analysed on an endpoint basis, including only participants with a final assessment, or analysed using the last observation carried forward to the final assessment (LOCF) if LOCF data were reported by the trial authors. Where possible, exact SDs will be calculated from P values, t-values, confidence intervals or standard errors, when these are reported in articles (Altman and Bland 1996). Where no such information is available, attempts will be made to obtain these data through contacting trial authors. Where the vast majority of actual SDs are available and only a minority of SDs are unavailable or unobtainable, a method used for imputing SDs and calculating percentage responders devised by Furukawa and colleagues (Furukawa et al. 2006) will be used. We will check that the original standard deviations are properly distributed, so that the imputed standard deviation represents the average. Where this method is employed, data will be interpreted with caution, taking account of the degree of heterogeneity observed. A sensitivity analysis will also be undertaken 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.

Data synthesis

We will generate descriptive statistics for trial and study population characteristics across all eligible trials, describing the types of comparisons and some important variables, either clinical or methodological (such as year of publication, age, severity of illness, clinical setting).

Pairwise meta-analysis

For each pair-wise comparison between treatments, the odds ratio will be calculated with a 95% CI. A standard, pairwise meta-analysis will be conducted for each pairwise comparison of treatments using RevMan. We anticipate some clinical heterogeneity between studies and so where there are ≥ 3 studies we plan to use a random-effects model to incorporate the assumption that the different studies are estimating different, yet related, treatment effects (DerSimonian and Laird 1986). Where there are < 3 studies we will combine in a fixed effect analysis (Mantel and Haenszel 1959).

As the correct interpretation of the pooled summary from a random effects analysis is an “average” effect across the studies, it can be difficult to apply to individual study settings (Riley et al. 2011). A prediction interval, which captures the uncertainty in the summary estimate, the estimate of the between study standard deviation (Tau) and the uncertainty in Tau (Higgins et al. 2009), will therefore also be estimated.

MTM

To ensure that the network is connected, a network diagram will be constructed for the primary outcome only. Note that MTM is only possible for a connected set of treatments.

A random-effects MTM, taking into account the correlations induced by multi-arm trials, will be conducted in a Bayesian framework and implemented using WinBUGS 1.4.1 (<http://www.mrc-bsu.cam.ac.uk/bugs/>). The probability that each treatment is the most effective at improving response will also be calculated. The goodness of fit of the model to the data will be measured by the posterior mean of the residual deviance. This is defined as the difference between the deviance for the fitted model and the deviance for the saturated model, where deviance measures the fit of the model to the data points using the likelihood function. We will examine

leverage plots to help identify any specific data points (trial arms) that were fitting poorly in each model. A leverage plot displays the leverage (a measure of influence equal to the contribution of each trial arm to P_D , the effective number of parameters) versus the signed, square root of the residual deviance (a measure of fit) for each data point. Points with a high leverage are influential, which means that they have a strong influence on the model parameters that generate their fitted values. Convergence will be assessed using two chains and based on the Brooks-Gelman-Rubin diagnostic tool in WinBUGS.

Unit of analysis issues

Studies with more than two intervention arms can pose analytical problems in pair-wise meta-analysis. Where studies have two or more active treatment arms to be compared against treatment as usual, data will be managed in this review as follows:

Continuous data: Means, SDs and number of participants for each active treatment group will be pooled across treatment arms as a function of the number of participants in each arm to be compared against the control group (Higgins 2008; Higgins 2008b; Law 2003).

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 between the treatment groups.

Assessment of heterogeneity

Pairwise meta-analyses

Visual inspection of the forest plots will be used to investigate the possibility of statistical heterogeneity. This will be supplemented using the I-squared statistic. This provides an estimate of the percentage of variability due to heterogeneity rather than a sampling error (Higgins et al. 2003). 95% confidence intervals will be calculated for I-squared, and a P value from a χ^2 test for heterogeneity will be used to assess evidence of its presence. We will also report Tau² (the between study variance). We consider a degree of heterogeneity inevitable and therefore only I² values $\geq 50\%$ will be explored further using subgroup analyses for the primary outcome only.

MTM

Inconsistency can be considered an additional layer of heterogeneity which can occur in networks of evidence. It can occur when there is a discrepancy between a direct and indirect estimate of treatment effect. As such inconsistency is considered a property of 'closed loops' of evidence. As a first step, we will calculate the difference between indirect and direct estimates in each closed loop formed by the network of trials as a measure of inconsistency and we will subsequently examine whether there are any material discrepancies. We will also use model fit statistics as an informal check of inconsistency. In case of considerable inconsistency we will investigate possible sources of it.

In the network meta-analysis we will assume homogeneous between study variability across studies (Lu and Ades 2004). We will report Tau (the standard deviation of underlying effects across studies) as our estimate of heterogeneity. We will also report the effective number of parameters, p_D , which increases with the degree of heterogeneity in the random effect models, and so can also be viewed as a measure of heterogeneity.

Assessment of reporting biases

As far as possible, the impact of reporting biases will be minimised by undertaking comprehensive searches of multiple sources (including trial registries), increasing efforts to identify unpublished material including contacts with the original study authors, and including non-English language publications.

We will also try and identify outcome reporting bias in trials by focusing on our predefined primary and secondary outcomes and using the imputation to increase the number of studies included in the review (Furukawa et al. 2007).

Pairwise meta-analyses

Only if there are greater than 10 studies per pairwise meta-analysis will we consider using funnel plots to assess the impact of reporting bias on the estimates of treatment effect. We will investigate the presence of small study effects for the primary outcomes only. For dichotomous outcomes several tests are available. Note that our choice of test for funnel plot asymmetry will depend on the degree of heterogeneity observed.

MTM

The assessment of reporting biases is a new area in network meta-analysis and no agreed methodology

currently exists. As such, we propose a simple approach to the evaluation of small study effects, and will conduct a sensitivity analysis excluding studies with sample ≤ 50 participants per arm. We will also use Tanaka's method [ref] and Chaimani's method (Chaimani and Salanti 2012) to assess small study effects in MTM.

Effect modifiers and investigation of heterogeneity

The following sources of possible clinical heterogeneity are listed a priori and will be examined as effect modifiers in the MTM.

1. Year of publication
2. Baseline depression severity: 17-item HAMD scores at baseline will be entered as a covariate.
3. Researcher allegiance in psychotherapy arms and sponsorship in pharmacotherapy arms

Sensitivity analysis

In order to examine if the obtained results are preserved when we limit the included studies to high quality ones only, we will examine the following variables.

1. Allocation concealment: Allocation concealment will be used as a marker of trial quality (Wood et al. 2008). Studies that were rated at high or unclear risk of bias for allocation concealment will be excluded.
2. Blinding: The influence of including open studies and single-blind studies will be examined.
3. Length of treatment: Four weeks may be too short to differentiate psychotherapies and pharmacotherapies. Studies will be limited to those whose outcomes are reported at 6 weeks or later.
4. Psychotherapy fidelity: Studies that were rated at high or unclear risk of bias for psychotherapy fidelity will be excluded.
5. If pharmacotherapy/GP visits allowed as a cointervention in psychotherapy arms
6. Imputation: Trials where missing data have been imputed will be excluded.

Results

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