The effect of cognitive therapy versus interpersonal psychotherapy in patients with major depressive disorder. A systematic review of randomised clinical trials with meta-analyses and trial sequential analyses

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Background

Depression
According to the WHO, major depressive disorder is the second largest healthcare problem worldwide in terms of disability caused by illness (Levav 2002). It afflicts an estimated of 17% of individuals during their lifetimes at tremendous cost to society (Greenberg 1990; Kessler 1994), and roughly a third of all depressive disorders take a chronic course (Spijker 2002; Arnow 2003). Compared to other medical disorders, depressive illness causes the most significant deterioration in individual life quality (Bech 1999). Approximately 15% of depressive patients will commit suicide over a 10-20 year period (Fawcett 1993).

Antidepressant medication
A number of depressive patients are treated with antidepressant medication, the efficacy of which has been studied in a number of meta-analyses and systematic reviews. In their 1996 meta-analysis, Joffe et al. found medical antidepressant treatment to be significantly more effective than placebo (Joffe 1996). Similarly, in 2004, Moncrieff et al. in their Cochrane review found that antidepressant medication was significantly more effective than ‘active’ placebo (Moncrieff 2004). ‘Active’ placebo is a placebo preparation that mimics the adverse effect profile of the preparation with which it is being compared, but without the ‘active’ placebo preparation having any actual beneficial effect on the disease. However, Moncrieff et al. also found that there is little difference between antidepressant medication versus active placebo and that the efficacy of antidepressant medication probably has been overestimated in studies where active placebo has not been used. A recently published review in the New England Journal of Medicine shows that randomised trials of new antidepressants remain largely unpublished if their results are neutral or negative (Turner 2008). Ninety-four percent of the published studies in the most widely-used databases showed a positive effect of the newer antidepressants. In the Food and Drug Administration (FDA) databases of
all randomised trials submitted to the FDA, only 51% of the trials demonstrated significant effects from the medication. When the unpublished trial results were added to the published ones, the updated meta-analyses showed no significant effects or very small significant intervention effects (Turner 2008). In the majority of the trials, either no intervention or inactive placebo was involved as comparator. Similarly, a meta-analysis of the total number of trials recently published by the Public Library of Science (PLoS), in which the unpublished trials were included, revealed that the new antidepressants had failed to demonstrate any significant beneficial effects on depression in patients with mild to moderate forms of the disease (Kirsh 2008). The meta-analysis revealed that significant effects from the new antidepressants were only achieved in severely depressed patients, and that this effect was clinically small (Kirsh 2008). However, this meta-analysis also included trials in which inactive placebo was used, which questions even this small effect. It is therefore clear that the efficacy of antidepressant medication is somewhat doubtful and immediately raises the question: are there other effective treatments for this very serious illness?

Psychotherapy

It is our clinical impression that a majority of depressed patients seek psychotherapeutic assistance. Many depressed patients want help to find the possible contributing causes for their depression, as well as the psychological tools to escape their suffering. A number of trials, particularly in recent years, have attempted to establish the clinical efficacy of psychotherapy – either as add-on therapy to the medical treatment, or as monotherapy (DeRubeis 2005; Dimidjian 2006).

Cognitive therapy and interpersonal therapy are the psychotherapeutic methods mostly studied in clinical trials for depression (Kessing 2006). Both interventions appear to be effective interventions for depression (Elkin 1989). We did not identify any systematic reviews or meta-analysis using Cochrane Collaboration methodology examining the effect of cognitive therapy versus interpersonal psychotherapy for major depressive
In a systematic review of randomised clinical trials involving meta-analyses (Cochrane Handbook for Systematic Reviews of Interventions, Higgins 2008) and trial sequential analyses (Wetterslev 2008; Brok 2008) we will try to answer the question: what are the beneficial and harmful effects of cognitive therapy versus interpersonal psychotherapy in the treatment of unipolar depression?

Objective
Based on a systematic review of the literature, to establish the beneficial and harmful effects of cognitive therapy versus interpersonal psychotherapy in the treatment of patients with major depressive disorder.

Criteria for studies included

Study design
Randomised clinical trials comparing cognitive therapy versus interpersonal psychotherapy in depressed patients, irrespective of language, publication status, and blinding.

Participants
Participants must be over 17 years, and the primary diagnosis must be major depressive disorder (i.e., unipolar depression).

The diagnosis of depression must be made based on one of the standardised criteria, such as DSM IV (APA 1994), ICD 10 (WHO 1992), DSM III (APA 1980), DSM III-R (APA 1987), or Feighner criteria (Feighner 1972). Comorbidity with other psychiatric diagnoses will not be an exclusion criterium. Participants suffering from serious somatic illness or depression during or after pregnancy will be excluded. Trials focusing on ‘late life’ depression or depression in participants with a drug or alcohol
dependence will also be excluded. This is done because we except participants in such trials to respond differently to standardised psychotherapy than other depressed patients, and these types of depressed patients are traditionally examined in separate trials.

**Interventions**

*Cognitive therapy*

Cognitive therapy is a collective term for a range of different forms of intervention and it is difficult to find a simple definition, which adequately describes this psychotherapeutic method. However, we have selected the following criteria as being necessary for the intervention to be classified as ‘cognitive therapy’:

**Contents in the cognitive therapy:**

1. That the intervention seeks to link thoughts, feeling and behaviour, and relates these to the depressive symptoms.
2. That the intervention seeks to record and correct any irrational thoughts or behavioural patterns, and relates this to the depressive symptoms.
3. That the intervention seeks to teach the patient alternative methods of thinking or behaving, and to be able to relate this to the depressive symptoms.
4. That the intervention is undertaken in either individual or group form.

Furthermore, the trials have to present a treatment manual and have to document adherence to the treatment manual.

Interventions that fulfil all criteria will be classified as ‘cognitive therapy’. All other trials that use the term ‘cognitive therapy’ will be included, but the intervention will be classified under ‘cognitive therapy, not adequately defined’.
**Interpersonal psychotherapy**

Interpersonal psychotherapy (IPT) is a structured form of psychotherapy that addresses interpersonal issues in depression. In order for the intervention to be classified as ‘interpersonal psychotherapy’ the intervention have to:

- Aim specifically to intervene on interpersonal disputes, role transitions, grief, and interpersonal deficits.
- Be undertaken face-to-face either individually or in a group.

Psychodynamic-interpersonal therapy is a modified form of interpersonal psychotherapy, but due to its similar characteristics to interpersonal psychotherapy we have chosen to include also trials assessing psychodynamic-interpersonal therapy.

Furthermore, the trials have to present a treatment manual and have to document adherence to the treatment manual.

Interventions that fulfil the above criteria will be classified as ‘interpersonal psychotherapy’. All other trials that use the term ‘interpersonal’ will be included, but the intervention will be classified under ‘interpersonal psychotherapy, not adequately defined’.

**Co-interventions**

Trials comparing cognitive therapy and interpersonal psychotherapy as add-on therapy to antidepressant medication will be included.

Trials comparing cognitive therapy and interpersonal psychotherapy as add-on therapy to electroconvulsive therapy (ECT) will be excluded. This is done because ECT cause short-term memory loss and therefore may minimise the potential effect of these therapies.

All other trials comparing cognitive therapy and interpersonal psychotherapy as add-on therapy to any kind of therapy will be included,
but only if this therapy is described and delivered similarly in the different intervention groups.

**Outcome measures**

**Primary outcome measures**

1. The mean value on follow-up using HAM-D (Hamilton’s depression scale, Hamilton 1960), BDI (Beck Depression Inventory, Beck 1961), or MADRS (Montgomery-Asberg Depression Rating Scale, Montgomery 1979).

All responses will be calculated based on the total number of randomised patients.

We will estimate therapeutic responses at two time points:
- Response at cessation of treatment. Often after 6-18 weeks of treatment. The trials original primary choice of completion date will be used. This is the most important outcome measure time point in this review.
- Response at follow-up: response at maximum follow-up.

2. Adverse events. We will classify adverse events as serious and non-serious. Serious adverse events are defined as medical events that are life-threatening, result in death, disability or significant loss of function; that cause hospital admission or prolonged hospitalisation or a hereditary anomaly or foetal injury. All other adverse events (that is, events that have not necessarily had a causal relationship with the treatment, but that resulted in a change in- or cessation of the treatment) will be considered non-serious events.

3. Quality of life. We will accept any measure of quality of life.

**Secondary outcome measures**
1. The proportion of patients achieving remission is calculated based on the total number of randomised patients. We have, pragmatically, defined remission as a Hamilton score of less than 8, BDI less than 10 or MADRS less than 10.

2. Number of suicides, suicide attempts or suicide inclination.

**Search methods**

We have chosen to search Psyk Info, the Cochrane Library’s CENTRAL, Medline via PubMed, EMBASE, Psychlit and Science Citation Index Expanded using the search words: “random*ed controlled trial” AND “cognitive” AND “depression” OR “depressive” AND “interpersonal”.

The timeframe for the search will be all trials published before February 2010.

**Selection of trials**

Two of the review authors will independently select relevant trials, based on criteria described in the above. If a trial only has been identified by one of the two, it will be discussed whether the trial should be included. If the two review authors disagree, a third review author will decide if the trial should be included. Excluded trials are entered on a list, stating the reason for exclusion.

**Data extraction**

The following data will be extracted from the included trials:

1. Date published.
2. Time frame of the trial period.
3. Inclusion- and exclusion criteria.
4. Whether a calculation of sample size has been published.
5. Number of research participants.
6. Number of included research participants.
7. Distribution of age and sex.
8. The extent of (respectively) the cognitive and the interpersonal intervention (individual or group; number of therapy-sessions).
9. Experience and education of the therapists (classified in 3 groups: low, intermediate or high).
10. Assess whether the trial-intervention should be classified as ‘adequately defined’ or ‘not adequately defined’ (see above).
11. Choice of outcome measures
12. Outcome measures.
13. Assessment of whether the relevant assessment methods include documentation of reliability.
14. Whether a protocol has been published before launch of randomisation.
15. The choice of method and an evaluation of the quality of this choice of method (see below).

Methods

We will use the instructions in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2008) in our evaluation of the methodology and hence bias risk of the included trials. Again, two review authors will assess the included trials independent of each other. We will evaluate the methodology in respect of generation of allocation sequence, allocation concealment, blinding, drop-outs, reporting of outcome measures, and other bias sources. This is done because these components enable classification of randomised trials with low risk of bias and high risk of bias. The latter trials overestimate positive intervention effects and underestimate negative effects (Kjaergard 2001; Gluud 2006; Woods 2008; Higgins 2008). We will classify the trials according to the components below:

Method for generating allocation sequence
Adequate: If randomising is performed by computer or a “random number table”. If the randomising is a random process, e.g., “heads or tails” or a throw of a dice; and the person performing the procedure in no other way is involved in the trial.
Uncertain: If the procedure in respect of randomising is not sufficiently described.
Inadequate: If the trial uses, e.g., date of admission or alternation for allocating the participants. Such trials will be included only in the assessment of harms.

Method of allocation concealment
Adequate: If the allocation sequence is concealed from the investigators, treatment providers and participants, for example by central randomisation. And this procedure is described and documented.
Uncertain: If the procedure to conceal allocation is not sufficiently described.
Inadequate: If the treatment providers/clinical principal investigators/study participants are able to predict the allocation sequence. Such trials will be included only in the assessment of harms.

Blinding
Because the intervention is psychotherapy, it is not possible to blind the treatment providers or trial participants. If an observer-dependent assessment method (Hamilton, for example) is used, it is possible to blind this observer. Personnel who supply or assess the observer-dependent questionnaires may also be blinded.

Adequate: If the personnel who instruct or supply or assess the observer-dependent questionnaire are blinded and this is described. Thus, personnel performing these procedures must not be otherwise involved in the trial
Uncertain: If the procedure of blinding is insufficiently described
Inadequate: If blinding is not performed or if the procedure cannot be classified as ‘adequate’ or ‘uncertain’.
Drop-outs
Adequate: If drop-outs following randomising can be described as being the same in the two intervention groups.
Uncertain: If drop-outs are not stated, or if the reasons why the participants dropped out are unclear.
Inadequate: If the pattern of drop-outs can be described as being different in the two intervention groups.

Reporting of outcome measures
Adequate: If all outcome measures are stated in the results. And the hierarchy of the efficacy variables are documented in a protocol before launch of randomisation.
Uncertain: If the method of choosing outcome measures is inadequately described.
Inadequate: If there is incongruence between the original protocol and the outcome measures used in the results, or if not all of the outcome measures are stated.

Comparability of characteristics at randomisation
Adequate: If the characteristics of the participants in the different intervention groups can be described as comparable before the start of intervention with regard to age, marital status, level of education, sex, diagnoses and severity of illness.
Uncertain: If the research participants’ characteristics have not been investigated as stated.
Inadequate: If there is suspicion that the characteristics of the intervention groups with regard to age, marital status, level of education, gender, diagnoses and severity of illness are not comparable, either by coincidence on randomising or due to bias in the case of drop outs (see above).

Stopped early
Adequate: If the trial is not stopped early. Or if it is stopped early based on formal or informal relevant stopping criteria.
Uncertain: If it is unclear whether the trial is stopped earlier than stated in the original protocol.
Inadequate: If the trial is stopped before the date stated in the original protocol.

**Economic bias**
Adequate: If the trial is not financed by an authority that might have an interest in a given result.
Uncertain: If there is no description of how the trial is financed.
Inadequate: If the trial is financed by an authority which could have an interest in a specific result from the trial.

**Academic bias sources**
Adequate: If the trialists do not have an academic/personal interest in a given result from the trial.
Uncertain: If there is no description of any academic interests that trialists might have.
Inadequate: If the trialists have a direct interest in a given result from the trial.

**Intention to treat**
Adequate: If intention to treat (ITT) analysis is preformed or allowed.
Uncertain: If it is unclear weather ITT is preformed or allowed.
Inadequate: If ITT analysis is not preformed or allowed.

**Statistical methods**
We will undertake this meta-analysis according to the recommendations stated in The Cochrane Collaboration Handbook (Higgins 2008). In analysing continues outcomes we will use the mean difference (MD) with a 95% confidence interval. We will use the risk ratio (RR) with a 95% confidence interval to estimate intervention effects on dichotomous
outcomes. We will perform funnel plot analysis in order to detect bias. For binary and continuous outcome measures, we will perform trial sequential analyses of results from the randomised trials (Wetterslev 2008; Brok 2008), in order to calculate the desired quantity of information and the cumulative Z-curve’s breach of relevant trial sequential monitoring boundaries. For binary outcomes we will estimate the required information size based on the proportion of patients with an outcome in the control group, a risk ratio suggested by the trials with low risk of bias, an alpha of 5%, a beta of 20%, and heterogeneity of 30% and 60%. For continuous outcomes we will estimate the required information size based on the standard deviation observed in the control group of trials with low risk of bias and a minimal relevant difference of 25% of this standard deviation, an alpha of 5%, a beta of 20%, and heterogeneity of 30% and 60%.

We planned to undertake four sub-group analyses:

1. We will investigate whether the therapists’ level of education/experience has an influence on the results.
2. We will investigate if there is a difference between the effects of group therapy and individual therapy.
3. We will investigate whether the results from the trials where the interventions were classified as ‘adequately defined’ differed from the trials with interventions that were classified as ‘not adequately defined’.
4. We will investigate whether the results from trials with low risk of bias differs from trials with uncertain- or high risk of bias. We define ‘low risk of bias’ as trials with adequate generation of the allocation sequence, adequate concealment of allocation, and allowing intention-to-treat analysis.
Literature


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Improvements of the protocol during the review process:

In August and September 2010 we made some improvements in our protocol originally published in February 2010. They encompassed:

1. The outcome hierarchy was changed. We included 'quality of life' and adverse events as a primary outcomes instead of a secondary outcomes, due to rereading the instructions of the Cochrane Handbook.
2. We changed our analysis of maximum follow-up response from “closest to 1 year” to “at maximum follow-up”
3. Suicide inclination was added to our secondary outcomes.
4. We improved our classification of a trial with ‘low risk of bias’, so our classification in cooperated all ten components of bias risk (see above).

None of these changes were data driven or caused any major changes to our conclusions.

In February 2011 we changed the title of the protocol. We changed ‘psychodynamic therapy’ to ‘interpersonal psychotherapy’ throughout the entire protocol. Originally we considered interpersonal psychotherapy as a contemporary form of psychodynamic therapy, but after careful consideration we decided to present our results regarding interpersonal psychotherapy versus cognitive therapy in a separate protocol.