

**The effect of psychodynamic therapy versus
treatment as usual 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 (i.e., unipolar depression) is the second largest healthcare problem worldwide in terms of disability caused by illness (Levav 2002). It afflicts an estimated 17% of individuals during their lifetimes at tremendous cost to society (Greenberg 1990; Kessler 1994). About 20% of depressions still persist after two years 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review in the New England Journal of Medicine shows that randomised trials of new antidepressants remain largely unpublished if their results are neutral or negative (Turner 2008).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).

Psychodynamic therapy

Psychodynamic therapy is the most commonly used form of psychotherapy in the Danish health-care system and has its origins back to Freud (Kessing 2006). It is often stated that psychodynamic therapy rarely has been examined in clinical trials (Kessing 2006), but we found no relevant

reviews in the Cochrane Library comparing the effect of psychodynamic therapy with no- intervention (search on: Depression AND psychodynamic in 'Title, abstract or keywords'). We found one relevant review examining the effect of psychodynamic therapy versus cognitive therapy for depression (Leichsenring 2001). In this review the authors included trials comparing the clinical effects of cognitive and psychodynamic therapy in treating currently depressed patients. The authors of the review conclude that the two interventions have comparable effects on almost all examined outcome measures (Leichsenring 2001). So do these results indicate that the two interventions are equally effective, or that they are equally ineffective?

Objective

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 psychodynamic therapy in the treatment of major depressive disorder compared with treatment as usual?

Criteria for trials included

Study design

Randomised clinical trials comparing psychodynamic therapy versus treatment as usual irrespective of language, publication status, and blinding.

Participants

Participants must be over 17 years, and the primary diagnosis must be major depressive disorder.

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). Co-morbidity 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 expect 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

Psychodynamic therapy

We have selected the following criteria as being necessary for the intervention to be classified as "psychodynamic therapy":

Contents in the psychodynamic therapy

That the trials use at least one of the following psychodynamic interventions:

1. The notions of transference and counter-transference (raising awareness of the therapeutic relationship).
2. Psychotherapeutic methods based on one of the classic developers of psychodynamic therapy such as Sifneos, Malan, Mann, Davanloo or Luborsky.
3. Trials using interpersonal psychotherapy (a special form of psychodynamic 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 'psychodynamic therapy'. All other trials that use the term 'psychodynamic' will be included, but the intervention will be classified under 'psychodynamic therapy, not adequately defined'. Trials involving 'interpersonal therapy' are classified under this designation.

Treatment as usual

Any non-specific treatment such as: treatment as usual, standard care, or clinical management. To be included the 'treatment as usual' condition as to include some kind of non-specific treatment. 'Waiting list' or interventions that can be classified as 'no intervention' will not be included.

Co-Interventions

Trials comparing psychodynamic therapy versus treatment as usual, as add-on therapy to antidepressant medication will be included. To be included the antidepressants have to be delivered similarly in the two intervention groups. These trials will be sub-grouped based on the type of antidepressant:

- Tricyclic antidepressants.
- Selective serotonin reuptake inhibitors (SSRI): citalopram, fluoxetine, sertraline, paroxetine, fluvoxamine, escitalopram.
- Serotonin noradrenalin reuptake inhibitors (SNRI): venlafaxine, duloxetine, milnacipran),
- Monoamine oxidase inhibitors (MAOI): phenelzine, tranylcypromine, isocarboxazid, selegiline
- Other antidepressants: mirtazapine, bupropion or reboxetine.

Trials comparing psychodynamic therapy 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 psychodynamic therapy.

All other trials comparing psychodynamic therapy versus treatment as usual, 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: "randomi*ed controlled trial" AND "psychodynamic" AND "depression"

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 the psychodynamic treatment (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 under 'Psychodynamic therapy', 'Psychodynamic therapy, 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 psychodynamic therapy, it is not possible to blind the treatment providers or trial participants. We therefore expect to find no trials comparing psychodynamic therapy with placebo or sham. 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 performed or allowed.

Uncertain: If it is unclear whether ITT is performed or allowed.

Inadequate: If ITT analysis is not performed or allowed.

Statistical methods

We will undertake this meta-analysis according to the recommendations stated in The Cochrane Collaboration Handbook (Higgins 2008). In analysing continuous 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 five sub-group analyses:

1. Cf. the above, we have chosen to include trials both with and without medical antidepressant treatment. We will investigate whether the results of psychodynamic therapy differs in these two groups of trials.
2. We will investigate whether the therapists' level of education/experience has an influence on the results.
3. We will investigate if there is a difference between the effects of group therapy and individual therapy.
4. We will investigate whether the results from the trials classified as, respectively, 'psychodynamic therapy" and 'Psychodynamic therapy, not adequately defined' differ from each other.
5. We will investigate whether the results from trials with low risk of bias differs from trials with uncertain- or high risk of bias.

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