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Review

The effect of adding psychodynamic therapy to antidepressants in patients with major depressive disorder. A systematic review of randomized clinical trials with meta-analyses and trial sequential analyses

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ABSTRACT

Background: Major depressive disorder afflicts an estimated 17% of individuals during their lifetimes at tremendous suffering and costs. Psychodynamic therapy may be a treatment option for depression, but the effects have only been limitedly assessed in systematic reviews.
Method: Using Cochrane systematic review methodology, we compared the benefits and harms of psychodynamic therapy versus 'no intervention' or sham for major depressive disorder. We accepted any co-intervention, including antidepressants, as long as it was delivered similarly in both intervention groups. Trials were identified by searching the Cochrane Library's CENTRAL, MEDLINE via PubMed, EMBASE, Psychlit, Psyc Info, and Science Citation Index Expanded until February 2010. Two authors independently extracted data. We evaluated risk of bias to control for systematic errors. We conducted trial sequential analysis to control for random errors.
Results: We included five trials randomizing a total of 365 participants who all received antidepressants as co-intervention. All trials had high risk of bias. Four trials assessed 'interpersonal psychotherapy' and one trial 'short psychodynamic supportive psychotherapy'. Meta-analysis showed that psychodynamic therapy significantly reduced depressive symptoms on the 17-item Hamilton Rating Scale for Depression (mean difference −3.01 (95% confidence interval −3.98 to −2.03; $P<0.00001$), no significant heterogeneity between trials) compared with 'no intervention'. Trial sequential analysis confirmed this result.
Limitations: Our results are based on few trials with high risk of bias and a limited number of participants so our results may be questionable.
Conclusions: Adding psychodynamic therapy to antidepressants might benefit depressed patients, but the possible treatment effect measured on the Hamilton Rating Scale for Depression is small.

Contents

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1. Introduction

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

Antidepressant medication remains the mainstay in the treatment of depression (Cipriani et al., 2009). A systematic review has shown that randomized trials of new antidepressants remain largely unpublished if their results are neutral or negative (Turner et al., 2008). When the unpublished trial results were added to the published ones, the updated meta-analyses showed no significant beneficial effect or only small significant beneficial intervention effects (Kirsch et al., 2008). Similarly, a meta-analysis of the total number of trials 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 (Kirsch et al., 2008). The meta-analysis showed that the new antidepressants only obtained beneficial effect in severely depressed patients, and that this effect was clinically small (Kirsch et al., 2008). Antidepressants are, however, known to decrease the risk of relapse of depression (Geddes et al., 2003). The therapeutic benefits of antidepressants seem to be limited and this raises the question if there are other effective treatments for this serious illness.

Psychodynamic therapy origins back to Freud (Trede, 2007). In some health-care systems, it is currently the most commonly used form of psychotherapy (Kessing et al., 2006). Psychodynamic therapy has rarely been examined in clinical trials (Kessing et al., 2006). We found only one meta-analysis examining the effect of psychodynamic therapy versus other treatments for depression (Driessen et al., 2010). The authors found that psychodynamic therapy generally is an effective treatment for depression (Driessen et al., 2010). However, the meta-analysis did not include assessment of bias risk in the included trials according to the recommendations in The Cochrane Handbook for Systematic Reviews of Interventions (Higgins and Green, 2008b), did not include trials using interpersonal psychotherapy as experimental intervention, and did not employ trial sequential analysis or other methods to reduce the risk of random errors (Driessen et al., 2010).

We therefore conducted a systematic review of randomized clinical trials involving meta-analysis (Higgins and Green, 2008b) and trial sequential analysis (Brok et al., 2008; Wetterslev et al., 2008) to answer the question: what are the beneficial and harmful effects of psychodynamic therapy versus 'no intervention' in the treatment of major depressive disorder?

2. Methods

For details regarding the methodology please consult our protocol published on our website (www.ctu.dk) in February 2010 before we began data extraction and analysis (Jakobsen et al., 2010). In short, we included all randomized clinical trials comparing the effect of psychodynamic therapy versus 'no intervention' with or without co-interventions — irrespective of language, publication status, publication year, and publication type. We searched in The Cochrane Library's CENTRAL, MEDLINE via PubMed, EMBASE, Psychlit, Psyc Info, and Science Citation Index Expanded. The timeframe for the search was all trials published before February 2010.

To be included participants had to be older than 17 years, and the primary diagnosis had to be major depressive disorder. Trials were only included if the diagnosis of depression was based on one of the standardized criteria, such as DSM IV (American Psychiatric Association, 1994), ICD

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10 (World Health Organization, 1992), DSM III (American Psychiatric Association, 1980), or DSM III-R (American Psychiatric Association, 1987). Co-morbidity with other psychiatric diagnoses was not an exclusion criterion. The following types of trials were excluded:

- Trials focusing on depressed participants with co-morbid serious somatic illness, e.g., myocardial infarction, multiple sclerosis, cerebral stroke, cancer, etc.
- Trials focusing on 'late life' depression or depression in the elderly, most often participants over 65 years.
- Trials focusing on pregnancy-related depression, e.g., postpartum depression, postnatal depression, etc.
- Drug or alcohol dependence-related depression.

These exclusions were conducted because we expect participants in such trials to respond differently to standardized psychotherapy than other depressed patients, and these types of depressed patients are traditionally examined in separate trials (Davidson et al., 2010; Howard et al., 2006; Sofuoglu et al., 2010; Wilkins et al., 2009).

To be included the trials had to use at least one of the following psychodynamic interventions:

- The notions of transference and counter-transference (raising awareness of the therapeutic relationship) (Hoglend et al., 2006).
- Psychotherapeutic methods based on one of the classic developers of psychodynamic therapy such as Sifneos, Malan, Mann, Davanloo, or Luborsky (Derksen, 2006).
- Trials using interpersonal psychotherapy (a contemporary form of psychodynamic therapy) (Cutler et al., 2004).

Furthermore, the trials had to present a treatment manual and had to document adherence to the treatment manual to be classified as 'psychodynamic therapy, adequately defined'. All other trials that used the term 'psychodynamic' were included, but the intervention was classified under 'psychodynamic therapy, not adequately defined'. In accordance, trials assessing 'interpersonal therapy' were classified under 'interpersonal psychotherapy, adequately defined' if they documented adherence to a treatment manual — and 'interpersonal psychotherapy, not adequately defined' if not.

Trials assessing the effect of antidepressants or any other alternative intervention, were included only if these co-interventions were described and administered similarly in the experimental and the control groups.

Two of the review authors (JJ and JLH) independently selected relevant trials. If a trial only was identified by one of the two, it was discussed whether the trial should be included. Excluded trials were entered on a list, stating the reason for exclusion.

2.1. Data extraction

Data were extracted for trial design, bias risk, and outcomes independently by two authors (JJ and JLH). Disagreements were resolved by discussion or through arbitration (CG). We used the instructions in The Cochrane Handbook for Systematic Reviews of Interventions (Higgins and Green, 2008b) in our evaluation of the methodology and hence bias risk of the trials. We assessed the bias risk in respect to:

Method for generating allocation sequence

Low risk of bias: If randomization was performed by a computer or a 'random number table', or if the randomization was a random process, e.g., 'heads or tails' or a throw of a dice.

Uncertain: If the procedure in respect of randomization was not sufficiently described.

High risk of bias: If the trial uses, e.g., date of admission or alternation for allocating the participants.

Method of allocation concealment

Low risk of bias: If the allocation sequence was concealed from the investigators, treatment providers and participants, for example by central randomization. And this is if this procedure was described and documented.

Uncertain: If the procedure to conceal allocation was not sufficiently described.

High risk of bias: If the treatment providers/clinical principal investigators/study participants were able to predict the allocation sequence.

Blinding

Because the intervention is psychodynamic therapy, it is not possible to blind the treatment providers or trial participants. But if an observer-dependent assessment method (e.g., HDRS) is used, it is possible to blind the observer. Personnel who supply or assess the observer-dependent questionnaires may also be blinded.

Low risk of bias: If the personnel who instructed or supplied or assessed the observer-dependent questionnaire were blinded and this was described.

Uncertain: If the procedure of blinding was insufficiently described.

High risk of bias: If blinding was not performed or if the procedure could not be classified as 'adequate' or 'uncertain'.

Drop-outs

Low risk of bias: If drop-outs following randomizing could be described as being the same in the two intervention groups.

Uncertain: If drop-outs were not stated, or if the reasons why the participants dropped out were unclear.

High risk of bias: If the pattern of drop-outs could be described as being different in the two intervention groups.

Reporting of outcome measures

Low risk of bias: If all outcome measures were stated in the results, and the hierarchy of the outcome measures were documented in a protocol before launch of randomization.

Uncertain: If the method of choosing outcome measures were inadequately described.

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High risk of bias: If there was incongruence between the original protocol and the outcome measures used in the results, or if not all of the outcome measures were reported.

Economic bias

Low risk of bias: If the trial was not financed by an authority that might have an interest in a given result.

Uncertain: If there was no description of how the trial was financed.

High risk of bias: If the trial was financed by an authority which could have an interest in a specific result from the trial.

Academic bias sources

Low risk of bias: If the trialists did not have an academic/personal interest in a given result from the trial, and this was stated.

Uncertain: If there was no description of any academic interests that the trialists might have.

High risk of bias: If the trialists did have an interest in a given result from the trial.

Intention to treat

Low risk of bias: If intention to treat (ITT) analysis was preformed or allowed.

Uncertain: If it is unclear whether ITT was preformed or allowed.

High risk of bias: If ITT analysis was not preformed or allowed.

The trials were overall classified as 'high risk of bias' if one or more of the above components were 'uncertain' or 'high risk of bias' (Gluud, 2006a, 2006b; Higgins and Green, 2008b; Wood et al., 2008). This classification is important because trials with 'high risk of bias' may overestimate positive intervention effects and underestimate negative effects (Gluud, 2006b; Higgins and Green, 2008b; Kjaergaard et al., 2001; Wood et al., 2008), and we wanted to relate the validity of our results to the risk of bias in the included trials.

2.2. Primary outcomes

2.2.1. Depressive symptoms

Our primary outcomes were the mean value on the Hamilton Rating Scale for Depression (HDRS) (Hamilton, 1960), Becks Depression Inventory (BDI) (Bech, 1961), or Montgomery-Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979). We included data based on the total number of randomized patients (intention-to-treat analysis) if these data were reported. We planned to estimate the therapeutic follow-up responses at two time points:

- At cessation of treatment: The trials' original primary choice of completion date was used. This was the most important outcome measure time point in this review.
- At maximum follow-up.

2.2.2. Adverse events

We classified adverse events as serious or non-serious. Serious adverse events were defined as medical events that result in death; are life threatening; or cause disability or significant loss of function; hospital admission or prolonged hospitalization; a hereditary anomaly; or fetal injury (ICH-GCP, 1997). 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) were considered as non-serious events.

2.2.3. Quality of life

We included any measure of quality of life noting each assessment measure.

2.3. Secondary outcomes

- The proportion of patients not having achieved remission. We included data based on the total number of randomized participants (intention-to-treat analysis) — if possible. If the results were not based on the total number of participants, we preformed an intention-to-treat analysis assuming that the participants not included in the results did not achieve remission (Higgins and Green, 2008b). We pragmatically defined remission as a HDRS of less than 8, BDI less than 10, or MADRS less than 10 (Bech, 1961; Hamilton, 1960; Montgomery and Asberg, 1979). These definitions are also the most commonly used.
- Number of suicides, suicide attempts, or records of suicide inclination.

2.4. Statistical methods

This meta-analysis was undertaken according to the recommendations in The Cochrane Handbook for Systematic Reviews of Interventions (Higgins and Green, 2008b). In analyzing continuous outcomes with both fixed-effect (DeMets, 1987) and with random-effects models (DerSimonian and Laird, 1986), we used the mean difference (MD) with a 95% confidence interval. We used RevMan version 5.0 for statistical calculations and analyses (The Nordic Cochrane Centre, 2008). We did not use 'standardized mean difference' so each outcome measure was analyzed separately. We did not adjust the outcome variables at follow-up according to the baseline values (Higgins and Green, 2008b).

We used the odds ratio (OR) with a 95% confidence interval to estimate intervention effects on dichotomous outcomes with both fixed-effect (DeMets, 1987) and with random-effects models (DerSimonian and Laird, 1986; The Nordic Cochrane Centre, 2008).

For the primary outcome measure, we also conducted trial sequential analysis. In order to calculate the required information size and the cumulative Z-curve's eventual breach of relevant trial sequential monitoring boundaries (Brok et al., 2008; Wetterslev et al., 2008), the required information size of the trial sequential analysis was based on a type I error of 5%, a beta of 10% (power of 90%), the variance of all the trials (as no trial had low risk of bias), and a minimal relevant difference of 2 points on the HDRS.

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3. Results

3.1. Search results

Our primary literature search identified 3212 publications. 2832 publications were excluded on the basis of the title or abstract, either because they did not relate to psychodynamic therapy and major depressive disorder or because they were not randomized trials comparing psychodynamic therapy versus 'no intervention'. Further 339 were excluded on the basis of the full publication, either because they did not relate to psychodynamic therapy and major depressive disorder or because they were not randomized trials comparing psychodynamic therapy versus 'no intervention'.

Further 13 publications (Bass et al., 2006; Bolton et al., 2003; Coulehan et al., 1997; de Arufo et al., 2000; Lang et al., 2006; Levkovitz et al., 2000; Maina et al., 2005; Miller and Weissman, 2002; Piper et al., 1990; Rodriguez et al., 2004; Simpson et al., 2000, 2003; Vitriol et al., 2009) were excluded because the trial participants did not meet our inclusion criteria.

We excluded 16 publications (Burnand et al., 2002; DiMascio et al., 1979; Elkin et al., 1985, 1989; Imber et al., 1990; Kech et al., 2008; Schramm et al., 2007, 2008; Schulberg et al., 1996; Sotsky et al., 1991; Stewart et al., 1998; Swartz et al., 2006, 2008; van et al., 2009; Weissman et al., 1979, 1981) on six trials (Burnand et al., 2002; DiMascio et al., 1979; Elkin et al., 1989; Schramm et al., 2007; Schulberg et al., 1996; Swartz et al., 2008) comparing psychodynamic therapy versus 'treatment as usual', 'standard care', or 'clinical management'. According to our protocol (Jakobsen et al., 2010) we excluded these trials from our analysis, because the control interventions were not delivered similarly in both intervention groups.

3.2. Included trials

We identified 12 publications (Bellino et al., 2006; Blom et al., 2007a, 2007b; De Jonghe et al., 2001; DiMascio et al., 1979; Kool et al., 2003a, 2003b; Kool et al., 2007; Molenaar et al., 2007; Weissman et al., 1979, 1981; Ye and Ming, 2006) on five trials (Bellino et al., 2006; Blom et al., 2007a; De Jonghe et al., 2001; DiMascio et al., 1979). The five trials included a total of 365 participants. The experimental interventions were termed 'interpersonal psychotherapy' in four trials (Bellino et al., 2006; Blom et al., 2007a; DiMascio et al., 1979; Ye and Ming, 2006) and 'short psychodynamic supportive psychotherapy' in one trial (De Jonghe et al., 2001).

The overall baseline characteristics in respect to age, sex, education, marital status, and baseline means, were assessed as being 'comparable' in two of the trials (Bellino et al., 2006; Blom et al., 2007a) and 'unclear' in three trials (De Jonghe et al., 2001; DiMascio et al., 1979; Ye and Ming, 2006) (Table 1). Only one of the trials used an experimental intervention that we classified as 'adequately defined' (Blom et al., 2007a). We classified the therapists' level of experience and/or education in three of the trials as 'intermediate' (Bellino et al., 2006; Blom et al., 2007a; De Jonghe et al., 2001) and in the remaining two as 'unclear' (DiMascio et al., 1979; Ye and Ming, 2006). Four trials used individual therapy (Bellino et al., 2006; Blom et al., 2007a; De Jonghe et al., 2001; DiMascio et al., 1979), and one trial used group therapy (Ye and Ming, 2006).

The duration of the experimental intervention varied in the five trials from 12 weeks (Blom et al., 2007a; Ye and Ming, 2006) to 24 weeks (Bellino et al., 2006) of treatment (Table 1).

All five trials used the experimental intervention psychodynamic therapy as add on therapy to antidepressants, and all trials used antidepressants in both the experimental and the control groups. The antidepressant medication was not adequately described in one trial (Ye and Ming, 2006). The antidepressant medicine was described and delivered similarly to the compared intervention groups in four of the trials (Bellino et al., 2006; Blom et al., 2007a; De Jonghe et al., 2001; DiMascio et al., 1979). The antidepressants were: flouxetine (SSRI) (Bellino et al., 2006); nefazodone hydrochloride (5H2 receptor antagonist) (Blom et al., 2007a); amitriptyline (TCA) (DiMascio et al., 1979); and fluoxetine, amitriptyline (TCA), and moclobemide (monoamine-oxydase inhibitor) (De Jonghe et al., 2001). No other co-interventions were documented.

Table 1 summarizes the characteristics of the five included trials.

3.3. Bias risk

We assessed all five trials as having 'high risk of bias' due to unclear or inadequate components as described in Table 2.

3.4. Effects of psychodynamic therapy

3.4.1. Primary outcome measures

Four trials assessed HDRS as a continuous outcome measure at the end of treatment. One trial (Blom et al., 2007a) also assessed MADRS.

Meta-analysis with fixed-effect model on the HDRS data from four trials (Bellino et al., 2006; Blom et al., 2007a; De Jonghe et al., 2001) shows that psychodynamic therapy plus antidepressants significantly reduced depressive symptoms at the end of treatment compared with antidepressants alone. We found a mean difference on −3.01 HDRS (95% CI −3.98 to −2.03; $P<0.00001$, $I^2=0$) (Fig. 1). The I^2 statistic describes the percentage of variation across trials that are due to heterogeneity rather than chance. Meta-analysis with random-effects model showed an identical result. None of the four trials included data after the assessment at cessation of treatment.

We performed a 'test of interaction' (Altman and Bland, 2003) to analyze if the effect of psychodynamic therapy differed between the three trials using 'interpersonal psychotherapy' (Bellino et al., 2006; Blom et al., 2007a; Ye and Ming, 2006) and the one trial using the term 'short psychodynamic supportive psychotherapy' (De Jonghe et al., 2001). 'Test of interaction' showed no significant difference ($P=0.65$) indicating that the effects of these two types of psychodynamic therapy do not seem to differ.

Trial sequential analysis also showed a significant beneficial effect of psychodynamic therapy plus antidepressants compared with antidepressants alone (Fig. 2).

One trial (DiMascio et al., 1979; Weissman et al., 1981) included records on hospitalizations. One participant in the

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Table 1
Characteristics of the included trials.

	Participants	Interventions/participant characteristics	Outcomes and comments
DiMascio et al., 1979	43	Interpersonal psychotherapy (individual 16 weeks) plus 100–200 mg amitriptyline versus 100–200 mg amitriptyline Participant characteristics Outpatients Age: <30 44%; 30–39; 28%; >40 27% Sex: 85% female, HDRS baseline means are not reported	HDRS and Raskin Depression Scale Diagnosis are based on Research Diagnostic Criteria (RDC) Data without SD values
De Jonghe et al., 2001	167	Short psychodynamic supportive psychotherapy (16 individual sessions in 24 weeks) plus 20 mg fluoxetine, 50–150 mg amitrityline, or 300–600 mg moclobemide versus 20 mg fluoxetine 50–150 mg amitrityline, or 300–600 mg moclobemide Participant characteristics Outpatients Age (total sample): 19–29 yr 34%; 30–39 yr 38%; 40–49 yr 20%;50–59 yr 6% Sex: 62% female HDRS at baseline (total sample): 20.43 (no significant difference between groups)	HDRS and% remission (HDRS <8) diagnosis: DSM-III-R
Bellino et al., 2006	32	Interpersonal psychotherapy (24 weekly individual sessions) plus 20–40 mg fluoxetine versus 20–40 mg fluoxetine Participant characteristics Outpatients Age (total sample): mean = 26.4 yr Sex: ratio of men to women 3 to 5 HDRS at baseline: 18.6 (control group) 19.6 (experimental group), no significant difference between groups	HDRS and% remission (see text for definition) Participants have co-morbidity with borderline personality disorder. It was unclear whether both intervention groups received similar clinical management.
Ye and Ming, 2006	60	Interpersonal psychotherapy (12 group-sessions) plus antidepressants versus antidepressants Antidepressant: type or dose not reported Participant characteristics Inpatients with educational background of middle school or above Age and sex not reported HDRS at baseline: experimental group = 21.33, control group = 21.60, no significant difference between groups	HDRS Chinese trial (translated)
Blom et al., 2007a, 2007b	96	Interpersonal psychotherapy (12–16 weeks of individual sessions) plus 100–600 mg nefazodone versus 100–600 mg nefazodone Participant characteristics Outpatients Age (mean): experimental group = 41 yr, control group 40 yr Sex: experimental group: 57.4% female, control Group: 68.1% HDRS at baseline: experimental group = 21.9, control group = 20.5 No significant differences on characteristics between groups	HDRS, MADRS, and% remission (HDRS<9) diagnosis: DSM-IV

experimental group and two in the control group were hospitalized. None of the remaining trials reported on adverse events.

One trial (De Jonghe et al., 2001) assessed Quality of Life Depression Scale (QLDS) (Hunt and McKenna, 1992) and found that the participants receiving psychodynamic therapy had significantly better scores than the control group. Another trial (Bellino et al., 2006) assessed Satisfaction Profile (SAT-P) for quality of life (Majani et al., 2000). The results showed a significant change on two (psychological functioning and social functioning) of the five factors in favor of psychodynamic therapy.

3.4.2. Secondary outcome measures

Three trials (Bellino et al., 2006; Blom et al., 2007a; De Jonghe et al., 2001) reported the proportion of participants without remission as a dichotomous outcome measure. We had planned to define remission as a HDRS of less than 8, BDI less than 10, or MADRS less than 10. However, this was only possible for (De Jonghe et al. 2001) (HDRS<8), so we adopted slightly different definitions:

- Bellino et al., 2006: a decreased HDRS score of 40% or more, final HDRS score <9, and a score of 1 or 2 on the improvement item of the Clinical Global Impression Scale (Berk et al., 2008).
- Blom et al., 2007a, 2007b: a final HDRS score <9.

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Table 2
Assessment of bias risk in the included trials.

	Adequate sequence generation	Allocation concealment	Intention to treat analysis	Adequate blinding	Comparability of drop-outs in intervention groups	Selective reporting of outcome-measures	Economic and academic bias	Overall assessment of 'risk of bias'
DiMascio et al., 1979	Unclear	Unclear	No	Yes	No	Unclear	Unclear	High
De Jonghe et al., 2001	Unclear	Unclear	Unclear	Yes	No	Unclear	Funded by Ely Lilly, academic bias unclear	High
Bellino et al., 2006	Unclear	Unclear	No	Yes	Yes	Unclear	No funding, academic bias unclear	High
Ye and Ming, 2006	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	High
Blom et al., 2007a, 2007b	Unclear	Unclear	No	Yes	Yes	Unclear	Unclear	High

Meta-analysis on the data from the three trials (Bellino et al., 2006; Blom et al., 2007a; De Jonghe et al., 2001) shows that psychodynamic therapy significantly decreases the odds ratio of 'no remission' to 0.41 (95% CI 0.24 to 0.73; P = 0.002, no heterogeneity) (Fig. 3). The number needed to treat to obtain one extra patient with remission is about five patients (95% CL 3 to 17).

One trial (DiMascio et al., 1979; Weissman et al., 1981) included records of suicides and suicide attempts. There were no suicides or suicide attempts. None of the remaining included trials reported the number of patients with suicide inclination, suicide attempts, or suicides.

3.4.3. Subgroup analyses

In subgroup analyses of therapists' level of education and experience (intermediate compared to unclear) and of type of therapy (group compared to individual), we found no significant difference on 'test of interaction' (Altman and Bland, 2003) and we found no heterogeneity in our results. This indicates that these factors do not seem to influence the effect of psychodynamic therapy.

In our protocol we had planned further subgroup-analyses according to risk of bias and antidepressant medication (Jakobsen et al., 2010). However, as all trials were classified as 'high risk of bias' and all trials used antidepressants as co-intervention, it was not possible to conduct these subgroup analyses.

4. Discussion

The results of our systematic review with meta-analysis and trial sequential analysis show that adding psychodynamic therapy to antidepressants may reduce depressive symptoms on the HDRS and may increase the probability of remission, compared with antidepressants alone. Our results are threatened by the fact that all trials had high risk of bias. If our results are valid, the number needed to treat to obtain one extra patient with remission is about five patients (95% CI 3 to 17).

This review has a number of strengths. Our protocol was published before we began the systematic literature searches in all relevant databases, data extraction, and data analyses. Data was extracted by two independent authors minimizing the risk of inaccurate data-extraction, and we assessed the risk of bias in all trials according to the guidelines in The Cochrane Handbook for Systematic Reviews of Interventions (Higgins and Green, 2008b). We meta-analyzed data both with fixed-effect and random-effects models and both analyses were in agreement in all our analyses. Furthermore, we performed trial sequential analysis to control for random errors (Brok et al., 2008; Wetterslev et al., 2008). The results

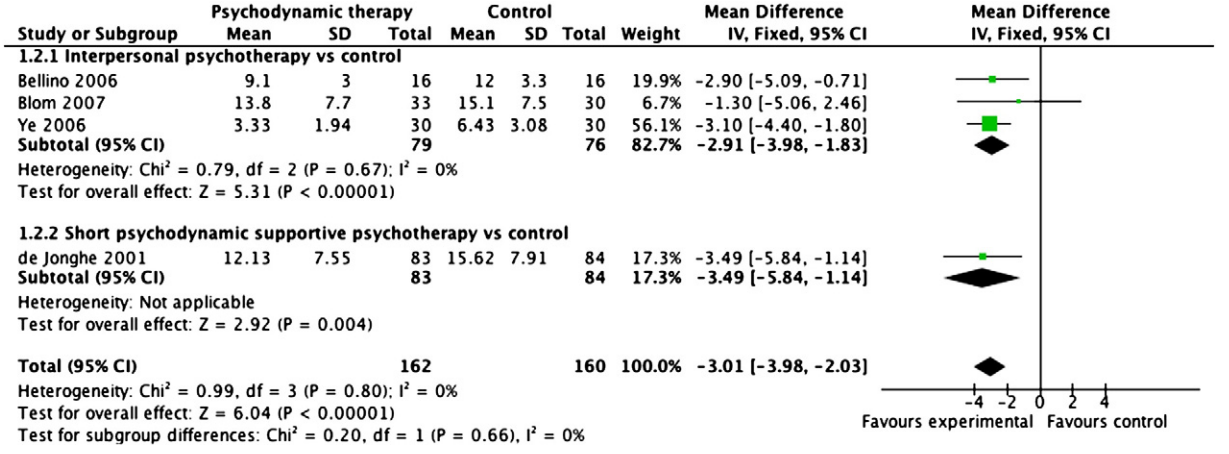

Fig. 1. The effect of psychodynamic therapy at cessation of treatment on Hamilton Rating Scale for Depression.

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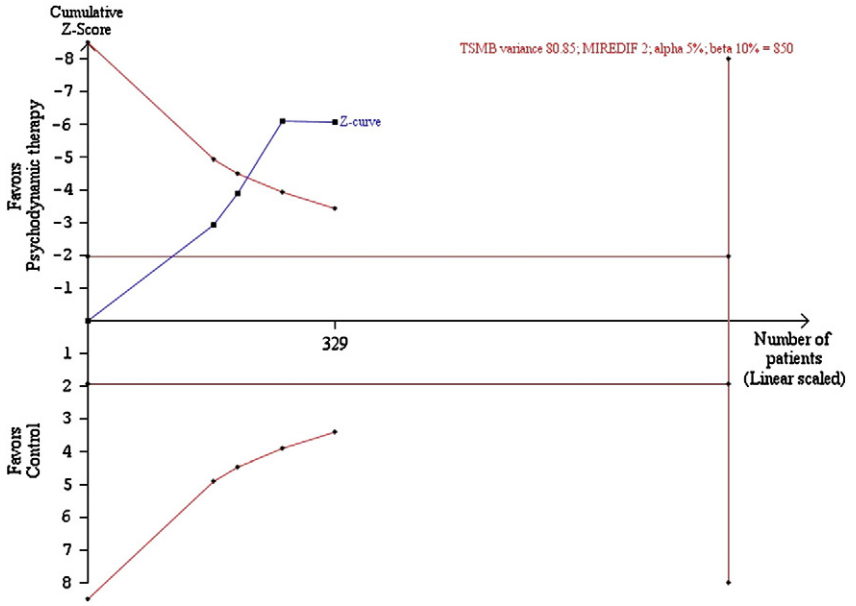

Fig. 2. Trial sequential analysis of the cumulative meta-analysis of the effect of psychodynamic therapy versus no treatment for depression. The required information size of 850 participants is calculated based on an intervention effect compared with no intervention of 2 points on the HDRS, a variance of 80.85 on the mean difference, a risk of type I error of 5% and a power of 90%. Even with these presumptions, the cumulated Z-curve (blue curve) crosses the trial sequential monitoring boundaries (red inner sloping lines) implying that there is firm evidence for a beneficial effect of psychodynamic therapy compared with no intervention. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

of the trial sequential analysis confirmed the result from the cumulative meta-analysis.

The characteristics of the participants as well as the severity of the depressive symptoms differed. e.g., the participants in one of the trials had co-morbidity with borderline personality disorder (Bellino et al., 2006), and another trial randomized inpatients (Ye and Ming, 2006). The included trials used different antidepressants (Table 1), and we chose to include trials both assessing interpersonal psychotherapy, which is a special form of psychodynamic therapy, and psychodynamic psychotherapy. We did not, however, find any heterogeneity in our analyses or differences with tests of interaction analyses. This indicates that there is a comparable treatment effect between the different forms of interventions and among the different populations. This may make our results more generally applicable.

Our systematic review has a number of limitations. Our results are based on only five trials with a limited number of participants and all of the trials had high risk of bias — so our results may be questionable. We limited our search to trials comparing psychodynamic therapy versus 'no intervention', and we can therefore not conclude anything about the effect of psychodynamic therapy versus other interventions. Only one of the trials (Blom et al., 2007a) used an intervention that we classified as 'adequately defined', i.e., using and documenting the use of a therapeutic manual. In clinical trials it is imperative that the interventions are adequately defined and described (Boutron et al., 2008). Factors like personal style, communication skills, and personality of the therapist evidently will influence the way psychotherapy is delivered (Walwyn and Roberts, 2010). It is difficult to describe and control for these subjective factors, and this makes it even more important to relate the therapy to a treatment manual. Otherwise it is unclear what kind of intervention the participants were receiving, and it is difficult to apply any given result in clinical practice. Moreover, a number of subgroups of depressed patients were not included in the trials of this review. These subgroups may react differently to psychotherapy and our results cannot be generalized to other than the patient groups included in the trials we identified.

According to The Cochrane Handbook for Systematic Reviews of Interventions we did not adjust our results according to baseline characteristics (Higgins and Green, 2008a). From the

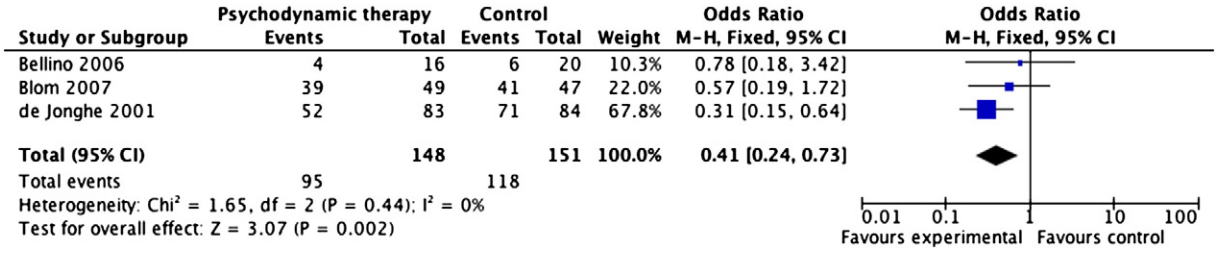

Fig. 3. Effect of psychodynamic therapy on remission. Events: participants not remitting.

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perspective of the meta-analysis, we also believe that the possible differences at baseline in the different intervention groups should be considered a random error (play of chance). With an increased number of trial participants and randomized trials this possible confounder will eventually even out between the compared intervention groups. The baseline characteristics (baseline means, age, sex, education, and marital status) were assessed as being 'comparable' in two of the included trials (Bellino et al., 2006; Blom et al., 2007a) and 'unclear' in three of the included trials (De Jonghe et al., 2001; DiMascio et al., 1979; Ye and Ming, 2006). Therefore, it is possible that the baseline characteristics were different in the experimental group and the control group in three of the trials. With a relatively limited number of included trials, this possible difference might influence our results and is a further limitation.

Primarily because we wanted to quantify the effect of psychodynamic therapy, any co-intervention had to be delivered similarly in the intervention groups. We found that the benefit from psychodynamic therapy, which is a relatively extensive treatment, was only a few points on the HDRS. From a clinical point of view it could be argued that this benefit is not clinically relevant — especially if you relate this mean difference to the extent and length of the intervention. On the other hand, our analyses demonstrate that the number needed to treat to obtain one extra patient in remission was only about five patients. However, this estimate was based on trials that primarily defined remission as a HDRS score under a given value. We believe it is questionable whether a single Hamilton score reflects true remission.

The HDRS might not be a useful instrument to quantify the effect of psychodynamic therapy. Other assessment-methods could demonstrate a more or less substantial effect of any given intervention for depression. Furthermore, severity of depression as measured by the total HDRS score has failed to predict suicide attempts (Chakraborty and Chatterjee, 2007), and some publications have questioned the usefulness of the HDRS and concluded that the scale is psychometrically and conceptually flawed (Bagby et al., 2004). The two other outcome measures often used to assess depressive symptoms MADRS and BDI probably correspond to HDRS (Fitzgibbon et al., 1988; Heo et al., 2007). The HDRS has during 40 years been considered the gold standard to quantify depressive symptoms in clinical trials (Bagby et al., 2004). There may be a need for other assessment methods.

None of the trials included assessments after the cessation of treatment. Therefore it is not clear whether psychodynamic therapy has an effect on depressive symptoms in the longer term.

Two of the trials reported two different measures of quality of life. Outcome measures of quality of life are generally not standardized and thoroughly individually validated (Higginson and Carr, 2001). The use of standardized outcome measures for quality of life in research has been limited by difficulties in administering and scoring quality of life (Higginson and Carr, 2001). For these reasons it is difficult to draw any definite conclusion on the basis of these two outcome measures for quality of life.

Typically adverse events are not reported as thoroughly as beneficial outcome measures (Hopewell et al., 2008), and psychological interventions might have harmful effects. Psychological debriefing for preventing post-traumatic stress disorder is one example (Rose et al., 2002). Debriefing has in some clinical trials shown to have a harmful effect (Rose et al., 2002). Only one of the included trials included records of suicide attempts, numbers of suicides, or adverse events. None of the included trials reported on suicide inclination. Possibly harmful effects of this kind of therapy are therefore not thoroughly examined.

In this review we chose to include trials comparing the effect of psychodynamic therapy versus 'no intervention'. If the trials involved any co-interventions they had to be applied similarly in the experimental and the control groups. A recent meta-analysis examining the effect of adding psychotherapy to antidepressants also found that combined treatment with psychotherapy and antidepressants was more effective than antidepressants alone (Cuijpers et al., 2009). Another recently published meta-analysis examined the effect of short-term psychodynamic psychotherapy for depression (Driessen et al., 2010). The results also showed a significant effect of short-term psychodynamic psychotherapy on depressive symptoms. The results from these two publications may support the validity of our results.

Future research should focus on comparing different forms of manualized psychodynamic therapy with 'no intervention' and with other treatments for depression. First and foremost such trials should be conducted with a low risk of systematic error (bias) and low risk of random error (play of chance) (Keus et al., 2010). Such trials should report on adverse events, suicide inclination, suicide attempts, and numbers of suicides, and should analyze the long-term beneficial and harmful effects of psychodynamic therapy. There seems to be a need for a new gold standard assessment method other than HRDS to assess depressive symptoms.

5. Conclusions

Adding psychodynamic therapy to antidepressants might benefit depressed patients, but the possible treatment effect on the HDRS is small. There is a need for randomized trials with low risk of bias, with low risk of random errors, and longer follow-up assessing both benefits and harms.

Role of the funding source

Nothing declared.

Conflicts of interest

None of the authors have any academic or economic interest in any given result of this review. JJ had access to all data and is responsibility for the integrity of the data and the accuracy of the data analysis.

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References

Altman, D.G., Bland, J.M., 2003. Interaction revisited: the difference between two estimates. BMJ 326 (7382), 219 available from: PM:12543843.

American Psychiatric Association, 1980. Diagnostic and Statistical Manual of Mental Disorders (DSM III).

American Psychiatric Association, 1987. Diagnostic and Statistical Manual of Mental Disorders (DSM III-R).

American Psychiatric Association, 1994. Diagnostic and statistical manual of mental disorders. Fourth update "text revision". DSM IV-TR.
Arnow, B.A., Constantino, M.J., 2003. Effectiveness of psychotherapy and combination treatment for chronic depression. Journal of Clinical Psychology 8, 893–905.
Bagby, R.M., Ryder, A.G., Schuller, D.R., Marshall, M.B., 2004. The Hamilton Depression Rating Scale: has the gold standard become a lead weight? American Journal of Psychiatry 161 (12), 2163–2177 available from: PM:15569884.
Bass, J., Neugebauer, R., Clougherty, K.F., Verdeli, H., Wickramaratne, P., Ndogoni, L., Speelman, L., Weissman, M., Bolton, P., 2006. Group interpersonal psychotherapy for depression in rural Uganda: 6-month outcomes: randomised controlled trial. British Journal of Psychiatry 188, 567–573.
Bech, A.T., 1961. An inventory for measuring depression. Archives of General Psychiatry (4), 561–571.
Bech, P., 1999. Stress & livskvalitet (Stress & Quality of Life). Psykiatrifondens Forlag.
Bellino, S., Zizza, M., Rinaldi, C., Bogetto, F., 2006. Combined treatment of major depression in patients with borderline personality disorder: a comparison with pharmacotherapy. Canadian Journal of Psychiatry 51, 453–460.
Berk, M., Ng, F., Dodd, S., Callaly, T., Campbell, S., Bernardo, M., Trauer, T., 2008. The validity of the CGI severity and improvement scales as measures of clinical effectiveness suitable for routine clinical use. Journal of Evaluation in Clinical Practice 14 (6), 979–983 available from: PM:18462279.
Blom, M.B., Jonker, K., Dusseldorp, E., Spinhoven, P., Hoencamp, E., Haffmans, J., van, D.R., 2007a. Combination treatment for acute depression is superior only when psychotherapy is added to medication. Psychotherapy and Psychosomatics 76, 289–297.
Blom, M.B., Spinhoven, P., Hoffman, T., Jonker, K., Hoencamp, E., Haffmans, P.M., van, D.R., 2007b. Severity and duration of depression, not personality factors, predict short term outcome in the treatment of major depression. Journal of Affective Disorders 104, 119–126.
Bolton, P., Bass, J., Neugebauer, R., Verdeli, H., Clougherty, K.F., Wickramaratne, P., Speelman, L., Ndogoni, L., Weissman, M., 2003. Group interpersonal psychotherapy for depression in rural Uganda: a randomized controlled trial. JAMA: Journal of the American Medical Association 289, 3117–3124.
Boutron, I., Moher, D., Altman, D.G., Schulz, K.F., Ravaud, P., 2008. Extending the CONSORT statement to randomized trials of nonpharmacologic treatment: explanation and elaboration. Annals of Internal Medicine 148 (4), 295–309 available from: PM:18283207.
Brok, J., Thorlund, K., Gluud, C., Wetterslev, J., 2008. Trial sequential analysis reveals insufficient information size and potentially false positive results in many meta-analysis. Journal of Clinical Epidemiology (61), 763–769.
Burnand, Y., Andreoli, A., Kolatte, E., Venturini, A., Rosset, N., 2002. Psychodynamic psychotherapy and clomipramine in the treatment of major depression. Psychiatric Services 53 (5), 585–590.
Chakraborty, R., Chatterjee, A., 2007. Predictors of suicide attempt among those with depression in an Indian sample: a brief report. The Internet Journal of Mental Health 4 (2).
Cipriani, A., Santilli, C., Furukawa, T.A., Signoretti, A., Nakagawa, A., McGuire, H., Churchill, R., Barbui, C., 2009. Escitalopram versus other antidepressive agents for depression. Cochrane Database of Systematic Reviews (2), CD006532 available from: PM:19370639.
Coulehan, J.L., Schulberg, H.C., Block, M.R., Madonia, M.J., Rodriguez, E., 1997. Treating depressed primary care patients improves their physical, mental, and social functioning. Archives of Internal Medicine 157, 1113–1120.
Cuijpers, P., Dekker, J., Hollon, S.D., Andersson, G., 2009. Adding psychotherapy to pharmacotherapy in the treatment of depressive disorders in adults: a meta-analysis. Journal of Clinical Psychiatry 70 (9), 1219–1229 available from: PM:19818243.
Cutler, J.L., Goldyne, A., Markowitz, J.C., Devlin, M.J., Glick, R.A., 2004. Comparing cognitive behavior therapy, interpersonal psychotherapy, and psychodynamic psychotherapy. American Journal of Psychiatry 161 (9), 1567–1573.
Davidson, K.W., Rieckmann, N., Clemow, L., Schwartz, J.E., Shimbo, D., Medina, V., Albanese, G., Kronish, I., Hegel, M., Burg, M.M., 2010. Enhanced depression care for patients with acute coronary syndrome and persistent depressive symptoms: coronary psychosocial evaluation studies randomized controlled trial. Archives of Internal Medicine 170 (7), 600–608 available from: PM:20386003.
de Arufo, C.B., Torres-Torija, C., Biagini Alarcon, M., Munoz, M.d.C.L., 2000. Effects of group psychotherapy in outpatients Spanish Psiquiatria 16 (2), 56.
De Jonghe, F., Kool, S., van, A.G., Dekker, J., Peen, J., 2001. Combining psychotherapy and antidepressants in the treatment of depression. Journal of Affective Disorders 64 (2), 217–229.
DeMets, D.L., 1987. Practical aspects in data monitoring: a brief review. Statistics in Medicine 6 (7), 753–760 available from: PM:3321314.
Derksen, J.J., 2006. Short-term psychodynamic psychotherapy. Tijdschrift voor Psychiatrie 48 (10), 777–786 available from: PM:17086942.
DerSimonian, R., Laird, N., 1986. Meta-analysis in clinical trials. Control Clinical Trials 7 (3), 177–188 available from: PM:3802833.
DiMascio, A., Weissman, M.M., Prusoff, B.A., Neu, C., Zwilling, M., Klerman, G.L., 1979. Differential symptom reduction by drugs and psychotherapy in acute depression. Archives of General Psychiatry 36, 1450–1456.
Driessen, E., Cuijpers, P., de Maat, S.C.M., Abbass, A.A., de, J.F., Dekker, J.J.M., 2010. The efficacy of short-term psychodynamic psychotherapy for depression: a meta-analysis. Clinical Psychology Review 30 (1), 25–36.
Elkin, I., Parloff, M.B., Hadley, S.W., Autry, J.H., 1985. NIMH treatment of Depression Collaborative Research Program: Background and research plan. Archives of General Psychiatry 42 (3), 305–316.
Elkin, I., Shea, M.T., Watkins, J.T., Imber, S.D., Sotsky, S.M., Collins, J.F., Glass, D.R., Pilkonis, P.A., Leber, W.R., Docherty, J.P., 1989. National Institute of Mental Health Treatment of Depression Collaborative Research Program. General effectiveness of treatments. Archives of General Psychiatry 46, 971–982.
Fawcett, J., 1993. The morbidity and mortality of clinical depression. International Clinical Psychopharmacology 8, 217–220.
Fitzgibbon, M.L., Cella, D.F., Sweeney, J.A., 1988. Redundancy in measures of depression. Journal of Clinical Psychology 44 (3), 372–374 available from: PM:3384963.
Geddes, J.R., Carney, S.M., Davies, C., Furukawa, T.A., Kupfer, D.J., Frank, E., Goodwin, G.M., 2003. Relapse prevention with antidepressant drug treatment in depressive disorders: a systematic review. Lancet 361 (9358), 653–661 available from: PM:12606176.
Gluud, C., 2006a. The culture of designing hepato-biliary randomised trials. Journal of Hepatology 44 (3), 607–615 available from: PM:16434120.
Gluud, L.L., 2006b. Bias in clinical intervention research. American Journal of Epidemiology (163), 493–501.
Greenberg, P., Stiglin, L.E., Finkelstein, S.N., Berndt, E.R., 1993. The economic burden of depression in 1990. Journal of Clinical Psychiatry 54, 405–418.
Hamilton, M., 1960. A rating scale for depression. Journal of Neurology, Neurosurgery & Psychiatry 23 (3), 56–61.
Heo, M., Murphy, C.F., Meyers, B.S., 2007. Relationship between the Hamilton Depression Rating Scale and the Montgomery-Asberg Depression Rating Scale in depressed elderly: a meta-analysis. American Journal of Geriatric Psychiatry 15 (10), 899–905 available from: PM:17911366.
Higgins, J., Green, S., 2008a. Cochrane Handbook for Systematic Reviews of Interventions, Version 5.0.0. Cochrane Collaboration.
Higgins, J., Green, S., 2008b. Cochrane Handbook for Systematic Reviews of interventions, Version 5.0.0. Cochrane Collaboration.
Higginson, I.J., Carr, A.J., 2001. Measuring quality of life: using quality of life measures in the clinical setting. British Medical Journal 322 (7297), 1297–1300 available from: PM:11375237.
Hoglend, P., Amlo, S., Marble, A., Bogwald, K.-P., Sorbye, O., Sjaastad, M.C., Heyerdahl, O., 2006. Analysis of the patient–therapist relationship in dynamic psychotherapy: an experimental study of transference interpretations. American Journal of Psychiatry 163 (10), 1739–1746.
Hopewell, S., Wolfenden, L., Clarke, M., 2008. Reporting of adverse events in systematic reviews can be improved: survey results. Journal of Clinical Epidemiology 61 (6), 597–602 available from: PM:18411039.
Howard, M., Battle, C.L., Pearlstein, T., Rosene-Montella, K., 2006. A psychiatric mother–baby day hospital for pregnant and postpartum women. Archives of Women's Mental Health 9 (4), 213–218 available from: PM:16718517.
Hunt, S.M., McKenna, S.P., 1992. The QLDS: a scale for the measurement of quality of life in depression. Health Policy 22 (3), 307–319 available from: PM:10122730.
ICH-GCP, 1997. Code of Federal Regulations & Guidelines Vol. 1. International Committee on Harmonization. Barnett International/PAREXEL, Philadelphia, US.
Imber, S.D., Pilkonis, P.A., Sotsky, S.M., Elkin, I., Watkins, J.T., Collins, J.F., Shea, M.T., Leber, W.R., Glass, D.R., 1990. Mode-specific effects among three treatments for depression. Journal of Consulting and Clinical Psychology 58, 352–359.
Jakobsen, J.C., Lindschou Hansen, J., Simonsen, E., Gluud, C., 2010. The effect of psychodynamic therapy versus no intervention in patients with major depressive disorder. A systematic review of randomised clinical trials with meta-analyses and trial sequential analyses. www.ctu.dk.
Kech, S., Zobel, I., Dykierek, P., van Calker, D., Berger, M., Schramm, E., 2008. Interpersonal psychotherapy for inpatients with depression. Effects on social adjustment and interpersonal problems German. References Zeitschrift fur Klinische Psychologie und Psychotherapie: Forschung und Praxis 37 (2), 81–88.
Kessing, L.V., Hansen, H.V., Hougaard, E., Hvenegaard, A., Albæk, J., 2006. Forebyggende ambulant behandling ved svær affektiv lidelse (depression og mani)- En medicinsk teknologi vurdering. Puljeprojekter 6 (9).

Please cite this article as: Jakobsen, J.C., et al., The effect of adding psychodynamic therapy to antidepressants in patients with major depressive disorder. A systematic review of r..., J. Affect. Disord. (2011), doi:10.1016/j.jad.2011.03.035

Kessler, R.C., McGnagle, K.A., Zhao, S., Nelson, C.B., Hughes, M., Eshleman, S., Wittchen, H.-U., Kendler, K.S., 1994. Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the united states: results from the Natinal Comorbidity Survey. Archives of General Psychiatry 51, 8–19.

Keus, F., Wetterslev, J., Gluud, C., van Laarhoven, C.J., 2010. Evidence at a glance: error matrix approach for overviewing available evidence. BMC Medical Research Methodology 10, 90 available from: PM:20920306.

Kirsch, I., Deacon, B.J., Huedo-Medina, T.B., Scoboria, A., Moore, T.J., Johnson, B.T., 2008. Initial severity and antidepressant benefits: a meta-analysis of data submitted to the Food and Drug Administration. PLoS Medicine 5.

Kjaergaard, L., Villumsen, J., Gluud, C., 2001. Reported methodologic quality and discrepancies between large and small randomized trials in meta-analysis. Annals of Internal Medicine 135 (11), 982–989.

Kool, S., Dekker, J., Duijsens, I.J., de, J.F., Puite, B., 2003a. Changes in personality pathology after pharmacotherapy and combined therapy for depressed patients. Journal of Personality Disorders 17 (1), 60–72.

Kool, S., Dekker, J., Duijsens, I.J., de, J.F., Puite, B., 2003b. Efficacy of combined therapy and pharmacotherapy for depressed patients with or without personality disorders. Harvard Review of Psychiatry 11, 133–141.

Kool, S., Schoevers, R., Duijsens, I.J., Peen, J., van, A.G., de, J.F., Dekker, J., 2007. Treatment of depressive disorder and comorbid personality pathology: combined therapy versus pharmacotherapy Dutch Tijdschrift voor Psychiatrie 49 (6), 361–372.

Lang, A.J., Norman, G.J., Casmar, P.V., 2006. A randomized trial of a brief mental health intervention for primary care patients. Journal of Consulting & Clinical Psychology 74 (6), 1173–1179.

Levav, I., Rutz, W., 2002. The WHO world health report 2001. New understanding—new hope. Israel Journal of Psychiatry & Related Sciences 39, 50–56.

Levkovitz, Y., Shahar, G., Native, G., Hirsfeld, E., Treves, I., Krieger, I., Fennig, S., 2000. Group interpersonal psychotherapy for patients with major depression disorder — pilot study. Journal of Affective Disorders 60, 191–195.

Maina, G., Forner, F., Bogetto, F., 2005. Randomized controlled trial comparing brief dynamic and supportive therapy with waiting list condition in minor depressive disorders. Psychotherapy and Psychosomatics 74, 43–50.

Majani, G., Pierobon, A., Giardini, A., Callegari, S., 2000. Satisfaction profile (SAT-P) in 732 patients: focus on subjectivity in hrqol assessment. Psychology and Health 15 (3).

Miller, L., Weissman, M., 2002. Interpersonal psychotherapy delivered over the telephone to recurrent depressives: a pilot study References Depression and Anxiety 16 (3), 117.

Molenaar, P.J., Dekker, J., Van, R., Hendriksen, M., Vink, A., Schoevers, R.A., 2007. Does adding psychotherapy to pharmacotherapy improve social functioning in the treatment of outpatient depression? Depression & Anxiety 24 (8), 553–562.

Montgomery, S.A., Asberg, M., 1979. A new depression scale designed to be sensitive to change. British Journal of Psychiatry 134, 382–389 available from: PM:444788.

Piper, W.E., Azim, H.F., McCallum, M., Joyce, A.S., 1990. Patient suitability and outcome in short-term individual psychotherapy. Journal of Consulting & Clinical Psychology 58 (4), 475–481.

Rodriguez, J.L., Butron, M.A.L., Terrez, B.E.V., Salcedo, V.V., 2004. Double blind study with antidepressant, brief psychotherapy and placebo in patients with mild to moderate depression (Spanish). Salud Mental 27 (5), 55–61.

Rose, S., Bisson, J., Churchill, R., Wessely, S., 2002. Psychological debriefing for preventing post traumatic stress disorder (PTSD) [2]. Cochrane Database.

Schramm, E., van, C.D., Dykierek, P., Lieb, K., Kech, S., Zobel, I., Leonhart, R., Berger, M., 2007. An intensive treatment program of interpersonal psychotherapy plus pharmacotherapy for depressed inpatients: acute and long-term results. American Journal of Psychiatry 164, 768–777.

Schramm, E., Schneider, D., Zobel, I., van, C.D., Dykierek, P., Kech, S., Härter, M., Berger, M., 2008. Efficacy of interpersonal psychotherapy plus pharmacotherapy in chronically depressed inpatients. Journal of Affective Disorders 109, 65–73.

Schulberg, H.C., Block, M.R., Madonia, M.J., Scott, C.P., Rodriguez, E., Imber, S.D., Perel, J., Lave, J., Houck, P.R., Coulehan, J.L., 1996. Treating major depression in primary care practice. Eight-month clinical outcomes. Archives of General Psychiatry. 53, 913–919.

Simpson, S., Corney, R., Fitzgerald, P., Beecham, J., 2000. A randomised controlled trial to evaluate the effectiveness and cost-effectiveness of counselling patients with chronic depression. Health Technology Assessment 4 (36) i + iii-74.

Simpson, S., Corney, R., Beecham, J., 2003. A randomized controlled trial to evaluate the effectiveness and cost-effectiveness of psychodynamic counselling for general practice patients with chronic depression. Psychological Medicine 33 (2), 229–239.

Sofuoglu, M., Sugarman, D.E., Carroll, K.M., 2010. Cognitive function as an emerging treatment target for marijuana addiction. Experimental and Clinical Psychopharmacology 18 (2), 109–119 available from: PM:20384422.

Sotsky, S.M., Glass, D.R., Shea, M.T., Pilkonis, P.A., 1991. Patient predictors of response to psychotherapy and pharmacotherapy: findings in the NIMH Treatment of Depression Collaborative Research Program. American Journal of Psychiatry 148 (8), 997–1008.

Spijker, J., de, G.R., Bijl, R.V., Beekman, A.T., Ormel, J., Nolen, W.A., 2002. Duration of major depressive episodes in the general population: results from The Netherlands Mental Health Survey and Incidence Study (NEMESIS). British Journal of Psychiatry 181, 208–213 available from: PM:12204924.

Stewart, J.W., Garfinkel, R., Nunes, E.V., Donovan, S., Klein, D.F., 1998. Atypical features and treatment response in the National Institute of Mental Health Treatment of Depression Collaborative Research Program. Journal of Clinical Psychopharmacology 18, 429–434.

Swartz, H.A., Zuckoff, A., Frank, E., Spielvogle, H.N., Shear, M.K., Fleming, M.A.D., Scott, J., 2006. An open-label trial of enhanced brief interpersonal psychotherapy in depressed mothers whose children are receiving psychiatric treatment References Depression and Anxiety 23 (7), 398–404.

Swartz, H.A., Frank, E., Zuckoff, A., Cyranowski, J.M., Houck, P.R., Cheng, Y., Fleming, M.A., Grote, N.K., Brent, D.A., Shear, M.K., 2008. Brief interpersonal psychotherapy for depressed mothers whose children are receiving psychiatric treatment. American Journal of Psychiatry 165, 1155–1162.

The Nordic Cochrane Centre, 2008. T. C. C. Review Manager (RevMan) [Computer program]. Version 5.0. The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen.

Trede, K., 2007. 150 years of Freud–Kraepelin dualism. Psychiatric Quarterly 78 (3), 237–240 available from: PM:17394082.

Turner, E.H., Matthews, A.M., Linardatos, E., Tell, R.A., Rosenthal, R., 2008. Selective publication of antidepressant trials and its influence on apparent efficacy. New England Journal of Medicine 358 (3), 252–260 available from: PM:18199864.

van,, C.D., Zobel, I., Dykierek, P., Deimel, C.M., Kech, S., Lieb, K., Berger, M., Schramm, E., 2009. Time course of response to antidepressants: predictive value of early improvement and effect of additional psychotherapy. Journal of Affective Disorders 114, 243–253.

Vitriol, V.G., Ballesteros, S.T., Florenzano, R.U., Weil, K.P., Benadof, D.F., 2009. Evaluation of an outpatient intervention for women with severe depression and a history of childhood trauma. Psychiatric services 60, 936–942.

Walwyn, R., Roberts, C., 2010. Therapist variation within randomised trials of psychotherapy: implications for precision, internal and external validity. Statistical Methods in Medical Research 19 (3), 291–315 available from: PM:19608603.

Weissman, M.M., Prusoff, B.A., DiMascio, A., Neu, C., Goklaney, M., Klerman, G.L., 1979. The efficacy of drugs and psychotherapy in the treatment of acute depressive episodes. American Journal of Psychiatry 136, 555–558.

Weissman, M.M., Klerman, G.L., Prusoff, B.A., Sholomskas, D., Padian, N., 1981. Depressed outpatients. Results one year after treatment with drugs and/or interpersonal psychotherapy. Archives of General Psychiatry 38 (1), 51–55.

Wetterslev, J., Thorlund, K., Brok, J., Gluud, C., 2008. Trial sequential analysis may establish when firm evidence is reached in cumulative meta-analysis. Journal of Clinical Epidemiology 61 (1), 64–75 available from: PM:18083463.

Wilkins, C.H., Mathews, J., Sheline, Y.I., 2009. Late life depression with cognitive impairment: evaluation and treatment. Journal of Clinical Interventions in Aging 4, 51–57 available from: PM:19503765.

Wood, L., Egger, M., Gluud, L.L., Schulz, K.F., Juni, P., Altman, D.G., Gluud, C., Martin, R.M., Wood, A.J., Sterne, J.A., 2008. Empirical evidence of bias in treatment effect estimates in controlled trials with different interventions and outcomes: meta-epidemiological study. British Medical Journal 336 (7644), 601–605 available from: PM:18316340.

World Health Organization, 1992. International Statistical Classification of Diseases an Related Health Problems (10th Revision) ICD 10. .

Ye, H.P., Ming, L., 2006. Group interpersonal psychotherapy for inpatient with major depression Chinese Chinese Mental Health Journal 20 (8), 526.

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