observation carried forward to the final assessment. A strict ITT analysis was not feasible with continuous outcomes, as the studies performed only LOCF or endpoint analyses.

### *Actual method*

Data were entered by TA into Review Manager 4.2.10 twice using the duplicate data entry feature. Analysis of dichotomous outcomes was planned, but only one study (Wu 2003) included this. Post-treatment scores were available in three studies (Wu 2003; Liossi 2001; Linn 1982) while change scores were available or could be calculated in six studies (Goodwin 2001; Classen 2001; Edelman 1999; Wood 1997; Linn 1982; Spiegel 1981). We therefore modified the data synthesis method during the review because the data obtained could not be synthesized appropriately using the planned method. The change between the baseline and immediate post-treatment scores was selected as the primary outcome for the meta-analysis (Banerjee 2006). The SMD and 95% CIs were pooled using a random-effects model (Alderson 2004). Two studies provided data on the results of slope analyses (Classen 2001; Spiegel 1981), and we calculated the change scores using these data. One paper provided raw data only (Wood 1997); for these data, we calculated the change score using SPSS 10.0J version software for Windows (SPSS 2003). In addition, because we could not obtain the actual figures for the standard deviations in the change scores for depression, anxiety, and general psychological distress in two studies (Classen 2001; Linn 1982), we calculated the pooled standard deviations in the other available studies that utilized the same measuring instrument (the Profile of Mood States) (MaNair 1992) (Edelman 1999; Goodwin 2001; Spiegel 1981; Wood 1997) and these values were inputted for the missing data (Furukawa 2006).

The heterogeneity among the studies was assessed using the $I^2$ and Q statistics and by visual inspection of the results in Meta View plots. An $I^2$ value greater than 30% or a Q statistic with a P value less than 0.1 were considered indicative of heterogeneity. If significant heterogeneity was suspected, the source of it was investigated.

### 5. Subgroup analyses

Subgroup analyses should be performed and interpreted with caution because multiple analyses can lead to false-positive conclusions (Oxman 1992). However, we performed the following subgroup analyses, if possible, for the following *a priori* reasons:

- A separate analysis was performed for participants who received group psychotherapy, since different modalities of psychotherapy (i.e., group versus individual) could have different effects.

- A separate analysis was performed for breast cancer patients, because many psycho-oncology studies focus on this patient group.

- A separate analysis was performed for participants with clinical depression based on any cut-off points or diagnostic criteria

of depression measures, because the effect of psychotherapy on depression may differ according to the baseline depressive status.

- A separate analysis was performed for participants receiving interventions by direct verbal or interactive communication delivered by health care professionals, or both, because this type of psychotherapy may have a different effect on depression.

### 6. Funnel plot analysis and sensitivity analyses:

- A funnel plot analysis was performed to check for any publication bias.

- A sensitivity analysis was performed, if possible, to examine the robustness of the observed findings by repeating all the analyses using only high-quality studies.

## DESCRIPTION OF STUDIES

Two independent review authors checked the studies identified by the search sources, and a total of 176 studies were extracted for possible inclusion. Full copies of these articles were obtained, and the two independent review authors then examined the strict eligibility of these papers. Further reference searches and a SciSearch did not yield any additional studies that satisfied the strict eligibility criteria. The inter-rater reliability of the strict eligibility criteria were as follows: kappa coefficient, 0.84, percent concordance, 95.5%.

First, we identified 16 studies that were potentially suitable for inclusion (Classen 2001; Edelman 1999; Giasson 1998; Goodwin 2001; Laidlaw 2005; Linn 1982; Liossi 2001; Mantovani 1996; North 1992; Sarna 1998; Schofield 2003; Sloman 2002; Soden 2004; Spiegel 1981; Wood 1997; Wu 2003). However, five of these studies (Giasson 1998; North 1992; Sarna 1998; Schofield 2003; Soden 2004) were ultimately dropped after a discussion among the review authors because the interventions in these studies were not forms of psychotherapy. The interventions in these studies were as follows: aromatherapy (Soden 2004), a multisensory environment (Schofield 2003), a structured nursing assessment of symptoms (Sarna 1998), noncontact therapeutic touch (Giasson 1998), and information provided by tape-recordings of consultations (North 1992). In addition, one study was excluded because of the absence of usual care in the control group (Mantovani 1996). Finally we identified ten studies that were suitable for inclusion (total of 780 participants) (Classen 2001; Edelman 1999; Goodwin 2001; Laidlaw 2005; Linn 1982; Liossi 2001; Sloman 2002; Spiegel 1981; Wood 1997; Wu 2003).

The subjects of the meta-analysis were recruited from three main groups: patients with metastatic breast cancer (five studies), patients who had received some form of palliative care (three studies), and various patients with advanced cancer (two studies).

Various types of interventions were utilized in these ten studies. Five studies (Classen 2001; Goodwin 2001; Linn 1982; Spiegel

1981; Wu 2003) mainly used supportive psychotherapy. Three studies mainly investigated the effect of behavioural therapies, either relaxation techniques (Sloman 2002) or hypnosis (Laidlaw 2005; Liossi 2001). The other studies used cognitive behavioural therapy (Edelman 1999) and problem-solving therapy (Wood 1997). The duration of the interventions was variable, ranging from just three to five sessions (Wood 1997) to unlimited and continuing until death (Spiegel 1981). Three of the five studies using supportive psychotherapy and the one study using cognitive behavioural therapy utilized group treatment sessions. Thus, the ten selected studies included several kinds of interventions, all of which involved direct verbal and interactive communication delivered by health care professionals (Classen 2001; Edelman 1999; Goodwin 2001; Laidlaw 2005; Liossi 2001; Linn 1982; Sloman 2002; Spiegel 1981; Wood 1997; Wu 2003). There were no interventions belonging to non-pharmacological interventions other than the aforementioned ones.

## METHODOLOGICAL QUALITY

With regard to study quality, none of the studies met the criteria for a 'good' rating. Three studies met the criteria for a 'fair' rating (Goodwin 2001; Linn 1982; Wu 2003), and the remaining seven studies were judged as having a 'poor' rating. Two studies clearly described the procedure for adequate allocation concealment (Goodwin 2001; Linn 1982).

## RESULTS

Two studies did not report the effects of the interventions on depression (Laidlaw 2005; Wood 1997), although they did measure the severity of depression among the participating subjects. As described above, all of the remaining eight studies used interventions involving direct verbal and interactive communication delivered by health care professionals (Classen 2001; Edelman 1999; Goodwin 2001; Linn 1982; Liossi 2001; Sloman 2002; Spiegel 1981; Wu 2003).

### Effects of psychotherapy on depression: meta-analyses

Moderate and statistically significant heterogeneity among six studies (see below) was observed (P = 0.004, $I^2$ = 71%). The identified studies were quite heterogeneous with regard to their participants and interventions, and many studies did not include some of the data required for meta-analyses. Consequently, we decided to conduct the meta-analyses by combining the data from studies in which the change scores were available. Thus, we excluded four studies because they did not contain necessary data, such as the change score, the standard deviation of the change score, or the number of participants (Laidlaw 2005; Liossi 2001; Sloman 2002; Wu 2003). The data from the six studies that provided all the information needed to conduct the meta-analyses were combined; all of these studies had used the Profile of Mood States as a measure of depression (Classen 2001; Edelman 1999; Goodwin 2001; Linn 1982; Spiegel 1981; Wood 1997). Among these six studies, four studies used supportive psychotherapy (Classen 2001; Goodwin 2001; Linn 1982; Spiegel 1981), one utilized cognitive behavioural therapy (Edelman 1999) and one utilized problem-solving therapy (Wood 1997). Regarding the data from the study by Linn et al., we decided to use the data obtained one month after intervention to minimize the effects of drop-outs, although the study provided data on depression at five time points during the intervention (Linn 1982).

The combined data from the six studies, involving 292 patients in the psychotherapy arm and 225 patients in the control arm, showed that psychotherapy had a significant effect on the treatment of depression among participants with advanced cancer (SMD = -0.44, 95% CI = -0.08 to -0.80). Visual inspection of the Meta View plots suggested that the study conducted by either Spiegel et al. or Wood et al. contributed most of the heterogeneity (Wood 1997; Spiegel 1981). While the heterogeneity indicators were similar if the study by Wood et al (Wood 1997) was excluded (Chi$^2$ = 15.49, df = 4 (P = 0.004), $I^2$ = 74%), the heterogeneity diminished and was no longer statistically significant if the study by Spiegel et al was excluded (Chi$^2$ = 5.93, df = 4 [P = 0.20], $I^2$ = 32.6%). The source of the heterogeneity was further investigated by examining the patient group, measuring instrument, type and duration of intervention, treatment of control group, outcome data and so on; however, clear factors that might have produced the heterogeneity could not be identified.

### Effect of psychotherapy on anxiety and general psychological distress: meta-analyses

Since one study did not measure anxiety (Linn 1982), we combined the data from five studies (Classen 2001; Edelman 1999; Goodwin 2001; Spiegel 1981; Wood 1997). The combined data, involving 242 patients in the psychotherapy arm and 169 patients in the control arm, showed that psychotherapy had a borderline effect on anxiety among participants with advanced cancer (SMD = -0.68, 95% CI = 0.01 to -1.37). Strong, statistically significant heterogeneity was observed (P < 0.00001, $I^2$ = 89.1%). Visual inspection of the Meta View plots suggested that the study conducted by Spiegel et al. was heterogeneous (Spiegel 1981). When this study was omitted, the significant heterogeneity was no longer observed (Chi$^2$ = 3.22, df = 3 [P = 0.36], $I^2$ = 6.8%).

Four studies provided data on general psychological distress, as evaluated using the total mood disturbance score of the POMS (Classen 2001; Edelman 1999; Goodwin 2001; Spiegel 1981). The combined data, involving 237 participants in the psychotherapy arm and 166 participants in the control arm, showed a significant effect for psychotherapy on general psychological distress among participants with advanced cancer (SMD = -0.94, 95% CI = -0.01 to -1.87). A strong, statistically significant heterogeneity was observed (P < 0.00001, $I^2$ = 94.3%). Visual inspection of the Meta View plots again suggested that the study conducted by

Spiegel et al. was heterogeneous (Spiegel 1981). When this study was omitted, the significant heterogeneity was no longer observed (Chi$^2$ = 2.43, df = 2 (P = 0.30), I$^2$ = 17.8%).

### Other secondary outcomes

We deleted some secondary endpoints, including symptom control, quality of life, coping measures for participants, and severity of physical symptoms (like pain), because few studies provided this kind of data. In addition, we stopped checking the tolerability of the treatment and the dichotomous outcomes for the same reason.

### Subgroup and sensitivity analyses

The two planned subgroup analyses (for participants who underwent group psychotherapy and for breast cancer patients) were conducted using the same four studies that investigated the effectiveness of group psychotherapy among metastatic breast cancer patients (Classen 2001; Edelman 1999; Goodwin 2001; Spiegel 1981). The results demonstrated similar and significant findings for all three targeted psychological symptoms: depression, anxiety, and general psychological distress.

The other subgroup analysis (for participants with clinical depression) was not conducted as none of the studies included the participants with clinically diagnosed depression. In addition, as described in the aforementioned section ('Effects of psychotherapy on depression: meta-analyses'), the planned subgroup analysis for participants receiving interventions via direct verbal and interactive communication delivered by health care professionals was not performed.

As only two studies included in the meta-analysis were judged to be of good or fair quality (Goodwin 2001; Linn 1982), a sensitivity analysis limited to these studies was performed. However, the study conducted by Linn et al. did not include anxiety and general psychological distress measures, so we conducted the sensitivity analysis for depression only. The combined data, involving 152 patients in the psychotherapy arm and 101 patients in the control arm, showed that psychotherapy was significantly effective for the treatment of depression (SMD = -0.35, 95% CI = -0.06 to -0.65). Statistically significant heterogeneity was not observed (P = 0.26, I$^2$ = 22.4%).

Although the number of included studies was small, thereby limiting the usefulness of a visual inspection of the funnel plot (Figure 01; Figure 02; Figure 03), a visual inspection did not suggest a prominent publication bias.

## DISCUSSION

### Current findings

This is the first systematic review, including a meta-analysis so far as we are aware, to show the significant effectiveness of verbal and interactive psychotherapeutic intervention for treating depression among advanced cancer patients. Unfortunately, the effectiveness of other types of non-pharmacological interventions for the treatment of depression could not be analysed because the available data on this topic was insufficient.

Our findings suggest that the effects of psychotherapy are almost comparable to those obtained in antidepressant pharmacotherapy studies in general psychiatry settings (Bech 2000). On the other hand, this effect was not consistent with a previous meta-analysis of 17 clinical trials that investigated the effect of psychological interventions on depression in cancer patients (Sheard 1999). This previous meta-analysis indicated an effect size of 0.19, suggesting a clinically weak or negligible effect. Since the subjects of the majority of the studies included in this previous meta-analysis were not advanced cancer patients and most of the studies had selected their patient populations based on cancer diagnosis, rather than on diagnostic or psychological criteria, or both, differences in the prevalence of clinical depression may be one possible explanation for the discrepancy between their meta-analysis and ours. In other words, since depression is common in patients with advanced cancer (see 'Background'), this difference may account for the different findings regarding the effect of the intervention.

Regarding the types of verbal and interactive psychotherapeutic interventions that were included in the meta-analysis, four of the six psychotherapeutic approaches utilized supportive therapy. Probably because of the nature of the study subjects (i.e., people suffering from incurable cancer), all of the approaches involved some form of techniques dealing with the impact of life-threatening disease on patients' lives, including issues of 'dying' or 'existence', or both, in addition to general support (Spiegel 1978; Yalom 1977). In addition, one of the most prominent characteristics of these four studies was the fact that the interventions essentially continued until the patients' deaths. On the other hand, specific types of psychotherapy, especially cognitive behavioural therapy, are widely recommended for the treatment of psychological distress among cancer patients; however, our systematic review highlights the need for more well-designed clinical trials to clarify the effectiveness of cognitive behavioural therapy on depression in patients with advanced cancer.

The findings with regard to anxiety and general psychological distress were similar to those for depression, although the results for anxiety did not reach statistical significance. These findings suggest that the psychotherapy may be useful for ameliorating a broad range of psychological distress, with the exception of anxiety experienced by advanced cancer patients.

### Clinical implications and future research

The present findings suggest that the depression experienced by advanced cancer patients, who are well-known to be at risk for developing depression or clinically profound psychological distress, or both, can be effectively ameliorated by psychotherapeutic intervention. Although our review could not clarify the cost effectiveness of psychotherapeutic interventions for patients with advanced cancer, and the fact that long-term continuous interven-

tions requiring trained mental health professionals may not be easy to provide for all patients, our findings suggest that psychological interventions should be combined with routine patient care for the treatment of patients with advanced cancer. At the same time, clarifying the cost-effectiveness of psychotherapy and developing cost-effective interventions for treating depression among advanced cancer patients may be important future tasks.

Some relevant questions remain concerning the effectiveness of psychotherapy on depression among patients with incurable cancer. First, because most studies included in the meta-analysis investigated the impact of the interventions just after or during the process of continuous treatment, or both, the persistent effects of the completed interventions were unclear. Second, because most of the subjects were not clinically diagnosed as having depression, the effectiveness of psychotherapy for the treatment of clinical depression could not be clarified in this review. These clinically important issues should be addressed in future studies.

Finally, we would like to comment on the study quality of the psychological interventions. As reported in the previous reviews, the quality of most of the studies was problematic (Newell 2002; Williams 2006). However, given the difficulty of conducting clinical trials in this population, such as in palliative care settings and of evaluating the quality of clinical trials for psychological interventions (Penrod 2004), novel and realistic quality assessment systems may be needed for studies focusing on patients with advanced cancer.

### Methodological advantages of this study
This systematic review has several major strengths. Firstly, we performed systematic and comprehensive literature searches for relevant studies, whereas previous studies contained several major flaws in their methodology, including a language bias (e.g., typically only English papers), and the combination of randomised and non-randomized clinical trials. Second, the *a priori* planned heterogeneity and sensitivity analyses indicated that the results of the analyses were quite robust.

### Limitations of this study
Our review also has some limitations. First, the reviewed studies generally had small sample sizes, and only a small number of studies (n = 6) were included in the meta-analysis. These factors may limit the validity of our findings. The existence of a possible outcome reporting bias cannot be negated (Chan 2005; Furukawa 2007). Secondly, although the use of data imputation for missing standard deviations of change scores was found to be valid in one study dealing with pharmacotherapy for depression (Furukawa 2006), whether this procedure was valid in our study sample was not confirmed. Thirdly, while this review included studies on the treatment of depression among advanced cancer patients, the results may not be applicable to advanced cancer patients with clinically diagnosed depression. Additionally, although this study also included meta-analyses for anxiety and general psychological distress, these findings were subsidiary and inconclusive. Finally,

because the subjects' physical status (e.g., physical functioning, estimated survival) were not clearly defined *a priori* and the participants were at least not critically terminally ill (i.e. an estimated survival period of less than a few months), the findings may not be applicable to end-stage cancer patients who are nearing death.

Despite these limitations, the obtained findings about the usefulness of psychotherapy for ameliorating depression in advanced cancer patients deserve important consideration, and future studies to investigate and clarify the usefulness of psychotherapy for treating clinically diagnosed depression in terminally ill patients are warranted.

## AUTHORS' CONCLUSIONS

### Implications for practice

Evidence from RCTs of moderate quality suggests that psychotherapy is useful for treating depressive states in advanced cancer patients although little evidence supports the effectiveness of psychotherapy for patients with clinically diagnosed depression including major depressive disorder. The effects of psychotherapy are almost comparable to those observed in antidepressant pharmacotherapy studies of major depressive disorders in general psychiatry settings. Regarding the types of verbal and interactive psychotherapeutic interventions, the most common approach was long-term continuous supportive therapy, typically until the patients' deaths. Although our review could not clarify the cost effectiveness of psychotherapeutic interventions for patients with advanced cancer and considering that long-term continuous interventions requiring trained mental health professionals may not be easy to provide for all patients, our findings suggest that psychological interventions should be combined with routine patient care for the treatment of patients with advanced cancer.

### Implications for research

The continuing effects of the completed interventions and the effectiveness of psychotherapy for the treatment of clinical depression should be addressed in future studies. In addition, clarifying the cost-effectiveness of psychotherapy and developing cost-effective interventions for the treatment of depression among advanced cancer patients are also important future tasks. Specific types of psychotherapy, especially cognitive behavioural therapy, are widely recommended for the treatment of psychological distress among cancer patients; however, our systematic review highlights the need for more well-designed clinical trials to clarify the effectiveness of cognitive behavioural therapy on depression in patients with advanced cancer. The effectiveness of psychotherapy for treating depression in end-stage cancer patients who are nearing death should also be investigated. Finally, given the difficulty of conducting clinical trials in palliative care settings and of evaluating the quality of clinical trials for psychological interventions,

novel and realistic quality assessment systems may be needed for studies focusing on patients with advanced cancer.

## POTENTIAL CONFLICT OF INTEREST

None known.

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# TABLES

## Characteristics of included studies

| Study | Classen 2001 |
| --- | --- |
| Methods | RCT |
| Participants | 125 women with metastatic breast cancer; American |
| Interventions | Supportive-expressive group psychotherapy, including fostering support among group members and encouraging the expression of emotions, psychoeducation, and self-hypnosis exercise (90 minutes weekly session lasting at least one year) |
| Outcomes | Profile of Mood States, Impact of Event scale |
| Notes | Quality score: 10 It is reported that the group therapy did not improve depression |
| Allocation concealment | B – Unclear |

| Study | Edelman 1999 |
| --- | --- |
| Methods | RCT |
| Participants | 124 women with metastatic breast cancer; Australian |
| Interventions | Group cognitive behavior therapy (8 weekly sessions) |

## Characteristics of included studies (*Continued*)

| Outcomes | Profile of Mood States, Coopersmith Self-esteem Inventory |
|---|---|
| Notes | Quality score: 7<br>It is reported that the therapy improved depression |
| Allocation concealment | B – Unclear |

| Study | Goodwin 2001 |
|---|---|
| Methods | RCT |
| Participants | 235 women with metastatic breast cancer; Canadian |
| Interventions | Supportive-expressive group psychotherapy, including fostering support among group members and encouraging the expression of emotions about cancer and its effects on their lives (90 minutes weekly session lasting at least one year) |
| Outcomes | Profile of Mood States, Pain scale, Suffering scale, Survival |
| Notes | Quality score: 17<br>It is reported that the group therapy improved depression |
| Allocation concealment | A – Adequate |

| Study | Laidlaw 2005 |
|---|---|
| Methods | RCT |
| Participants | 37 women with metastatic breast cancer; English |
| Interventions | 1. Self -hypnosis, including both anti-stress and anxiety techniques and visualization techniques (four weeks)<br>2. Johrei, a healing technique developed in Japan, is non-touch, and requires the practitioner to visualize healing light entering the body and being transferred via the outstretched hand to the recipient with a spirit of goodwill towards the other person (four weeks) |
| Outcomes | Beck Depression Inventory, Profile of Mood States Bi-Polar-Form, State Trait Anxiety Inventory, Impact of Event Scale, EORTC QLQ-C30, BR23<br>(Assessment was conducted after at least three months of practice) |
| Notes | Quality score: 5<br>The statistical results regarding depression were not reported |
| Allocation concealment | B – Unclear |

| Study | Linn 1982 |
|---|---|
| Methods | RCT |
| Participants | One hundred and twenty men with end-stage cancer (clinical stage IV) identified on wards of a large general hospital; American |
| Interventions | Counseling, including reducing denial, maintaining hope, life review, support for families<br>(several times a week till death) |
| Outcomes | Profile of Mood States, life satisfaction, self-esteem, alienation, locus of control<br>(one, three, six, nine, 12 months after the treatment) |
| Notes | Quality score: 13<br>It is reported that the therapy improved depression at three months |
| Allocation concealment | A – Adequate |

| Study | Liossi 2001 |
|---|---|
| Methods | RCT |
| Participants | Fifty terminally ill cancer patients who were referred for palliative care; Greek |

## Characteristics of included studies (*Continued*)

| Interventions | Hypnosis, including induction, suggestions for symptom management and ego-strengthening, and post hypnotic suggestions for comfort and maintenance of the therapeutic benefits<br>(30-minutes four weekly sessions) |
|---|---|
| Outcomes | Hospital Anxiety and Depression scale, Rotterdam Symptom Checklist<br>(four weeks after the start of the treatment) |
| Notes | Quality score: 9<br>It is reported that the therapy improved depression |
| Allocation concealment | B – Unclear |

| Study | **Sloman 2002** |
|---|---|
| Methods | RCT |
| Participants | Fifty six advanced cancer patients receiving home palliative care who were experiencing anxiety and depression; Australian |
| Interventions | Progressive muscle relaxation and guided imagery<br>(twice weekly) |
| Outcomes | Hospital Anxiety and Depression scale, Functional Living Index-Cancer scale<br>(three weeks after the initial session) |
| Notes | Quality score: 4<br>It is reported that significant positive changes occurred for depression |
| Allocation concealment | B – Unclear |

| Study | **Spiegel 1981** |
|---|---|
| Methods | RCT |
| Participants | Eighty six women with metastatic breast cancer; American |
| Interventions | Psychological support group, including fostering support among group members and encouraging the expression of emotions (90 minutes weekly session lasting at least one year) |
| Outcomes | Profile of Mood States, Rotter Internal/External Locus of Control Scale, Health Locus of Control Scale, Self-esteem (from the Janis-Field Scale), Maladaptive coping response, Phobias, Denial |
| Notes | Quality score: 9<br>The original study revealed "The treatment group tended (although not significantly) to be less depressed" on the basis of the findings about slopes analysis that investigated the score change per 100 days. On the other hand, because we set the outcome at the end of the study in the protocol, we recalculated the score change during 300 days. Consequently the score change has become to be statistically significant. |
| Allocation concealment | B – Unclear |

| Study | **Wood 1997** |
|---|---|
| Methods | RCT |
| Participants | Twenty cancer patients who were referred to hospice home care teams; English |
| Interventions | Problem-solving therapy<br>(three to five sessions) |
| Outcomes | Profile of Mood States, Hospital Anxiety and Depression scale, modified Social Adjustment Scale |
| Notes | Quality score: 9<br>The statistical results regarding depression were not reported |
| Allocation concealment | B – Unclear |

| Study | Wu 2003 |
|---|---|
| Methods | RCT |
| Participants | One hundred and twenty lung cancer patients receiving chemotherapy combined with radiotherapy; Chinese |
| Interventions | Supporting psychotherapy, including cognitive therapy, patient self-help group, behavioral therapy, and family education |
| Outcomes | Self-Rating Depression Scale, Self-Rating Anxiety Scale |
| | (one month after the start of the treatment ) |
| Notes | Quality score: 12 |
| | It is reported that the patients of the treatment group made a significant progress in relieving the depression compared with the control group |
| Allocation concealment | B – Unclear |

## Characteristics of excluded studies

| Study | Reason for exclusion |
|---|---|
| Edmonds 1999 | Although the POMS-Short Form was used as a psychological measure, this questionnaire cannot assess depression |
| Giasson 1998 | The intervention (noncontact therapeutic touch) was not considered as psychotherapy |
| Mantovani 1996 | The study did not include the usual care in the control group |
| North 1992 | The intervention (information giving by tape-recording the consultation) was not considered as psychotherapy |
| Sarna 1998 | The intervention (structured nursing assessment of symptom) was not considered as psychotherapy |
| Schofield 2003 | The intervention (use of multisensory environment [Snoezelen]) was not considered as psychotherapy |
| Soden 2004 | The intervention (aromatherapy, including massages with lavender essential oil and an inert oil) was not considered as psychotherapy |

**Table 01. Additional search strategies**

| Database searched | Search strategy used |
|---|---|
| PaPaS TRIALS REGISTER | (([psychotherapy OR psychotherap* OR aromatherapy* OR "art therapy" OR "autogenic training" OR "behavior* therapy" OR "behaviour* therap*" OR (biofeedback AND psycho*) OR "cognitive therapy" OR "cognitive behavioural therap*" OR (desensiti* AND psychol*) OR "implosive therapy" OR "relaxation therap*" OR "relaxation technique" OR "therapeutic touch" OR "touch therap*" OR yoga OR bibliotherapy OR "colour therap*" OR "colour therapy" OR "music therapy" OR hypnotherapy OR (imagery AND psychotherapy*) OR counsel* OR "group therap*" OR "socioenvironmental therapy" OR "socio-environmental therapy" OR "milieu therapy" OR "therapeutic community" OR "family therap*" OR psychosoc* OR psycholog* OR "self help group*" OR "support group*" OR "guided imagery") AND (depression OR depressive$ OR depressed) AND (neoplasms OR tumor$ OR tumour$ OR cancer$ OR carcinoma$ OR malignan$ OR neoplas$)) |
| CENTRAL | #1 PSYCHOTHERAPY (explode all trees MeSH) |
| | #2 (psychotherap* or aromatherap* or (art next training) or (behavior* near therap*) or (behaviour* near therap*) or (biofeedback and psycho*) or (cognitive near therap*) or (desensiti* and psychol*) or (implosive near therap*) or (relax* near therap*) or (relax* near techniq*) or (therap* near touch*) or yoga) |
| | #3 (bibliotherapy or (color* near therap*) or (colour* near therap*) or (music* near therap*) or (hypno* near therap*) or (imagery AND psychotherap*) or counsel* or (group* NEAR therap*) or (socioenvironmental next therap*) or (socio next environmental next therap*) or (milieu next therap*) or (therapeutic communit*) or (famil* near therap*) or psychosoc* or psycholog* or support* NEAR group* or guide* NEAR image*) |
| | #4 (#1 or #2 or #3) |
| | #5 DEPRESSION (single term MeSH) |
| | #6 (depression or depressive* or depressed) |
| | #7 (#5 or #6) |
| | #8 NEOPLASMS (explode all trees MeSH) |
| | #9 (tumor* or tumour* or cancer* or carcinoma* or malignan* or neoplas*) |
| | #10 (#8 or #9) |
| | #11 (#4 and #7 and #10) |
| EMBASE via Embase.Com | ((('psychotherapy'/exp AND [embase]/lim) OR ((psychotherap* OR aromatherap* OR 'art therapy' OR 'autogenic training' OR 'behavior therapy' OR 'behavioural therapy' OR ('biofeedback AND psycho*) OR 'cognitive therapy' OR 'cognitive behavioural therapy' OR 'cognitive behavioural therapies' OR (desensiti* AND psychol*) OR 'implosive therapy' OR 'relaxation therapy' OR 'relaxation therapies' OR 'relaxation technique' OR 'relaxation techniques' OR 'therapeutic touch' OR 'touch therapy' OR 'touch teherapies' OR 'yoga') AND [embase]/lim AND [embase]/lim) OR ((bibliotherapy OR 'color therapy' OR 'colour therapy' OR 'color therapies' OR 'colour therapies' OR 'music therapy' OR 'hypnotherapy' AND imagery AND psychotherap* OR counsel* OR 'group therapy' OR 'group therapies' OR 'socioenvironmental therapy' OR socio environmental therapy' OR 'milieu therapy' OR 'therapeutic community' OR 'family therapy' OR 'family therapies' OR psychosoc* OR psycholog* OR 'self help group' OR 'self help groups' OR 'support group' OR 'support groups' OR 'supportive groups' OR 'guided imagery') AND [embase]/lim) AND ((depression OR depressive* OR depressed AND [embase]/lim) OR ((depression/exp AND [embase]/lim) OR ((neoplasm'/exp AND [embase]/lim) OR ((tumor* OR tumour* OR cancer* OR carcinoma* OR malignan* OR neoplas*) AND [embase]/lim)) AND (('neoplasm'/exp AND [embase]/lim) OR ((tumor* OR tumour* OR cancer* OR carcinoma* OR malignan* OR neoplas*) |

## Table 01. Additional search strategies  (Continued)

| Database searched | Search strategy used |
|---|---|
| | AND [embase]/lim)) |
| | The above subject search was linked to the following Filter for EMBASE via EMBASE.com |
| | ((random*:ti,ab) OR (factorial*:ab,ti) OR (crossover*:ab,ti OR 'cross over*:ab,ti OR 'cross over':ab,ti) OR (placebo*:ab,ti) OR ('double blind' OR 'double blind') OR ('single blind':ab,ti OR 'single blind':ab,ti) OR (assign*:ti,ab OR allocat*:ti,ab) OR (volunteer*:ab,ti) OR ('randomized controlled trial'/exp AND [embase]/lim) OR ('single blind procedure'/exp AND [embase]/lim) OR ('double blind procedure'/exp AND [embase]/lim) OR ('crossover procedure'/exp AND [embase]/lim) NOT ((animal/ OR nonhuman/ OR 'animal'/de AND experiment/ AND [embase]/lim) NOT ((human/ AND [embase]/lim) AND (animal/ OR nonhuman/ OR 'animal'/de AND experiment/ AND [embase]/lim)) AND [embase]/lim) AND [embase]/lim |
| CINAHL via OVID | (Search Strategy as for MEDLINE but run with the following filter for Controlled Trials in CINAHL) |
| | 1. Random Assignment/ |
| | 2. single-blind studies/ |
| | 3. Double-Blind Studies/ |
| | 4. Triple-Blind Studies/ |
| | 5. Crossover Design/ |
| | 6. Factorial Design/ |
| | 7. (multicentre study or multicenter study or multi-centre study or multi-center study).mp. [mp=title, cinahl subject headings, abstract, instrumentation] |
| | 8. random$.ti,ab. |
| | 9. latin square.ti,ab. |
| | 10. cross-over.mp. or crossover.ti,ab. [mp=title, cinahl subject headings, abstract, instrumentation] |
| | 11. Placebos/ |
| | 12. ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab. |
| | 13. placebo$.mp. [mp=title, cinahl subject headings, abstract, instrumentation] |
| | 14. Clinical Trials/ |
| | 15. (clin$ adj25 trial$).mp. [mp=title, cinahl subject headings, abstract, instrumentation] |
| | 16. or/1-15 |
| PubMed Cancer Subset | #1 PSYCHOTHERAPY (MeSH) |
| | #2 (psychotherap* or aromatherap* or (art AND therap*) or (autogenic AND training) or (behavior* AND therap*) or (behaviour* AND therap*) or (biofeedback and psycho*) or (cognitive AND therap*) or (desensiti* and psychol*) or (implosive AND therap*) or (relax* AND therap*) or (relax* AND techniq*) or (therap* AND touch*) or yoga) |
| | #3 (bibliotherapy or (color* AND therap*) or (colour* AND therap*) or (music* AND therap*) or (hypno* AND therap*) or (imagery and psychotherap*) or counsel* or (group* AND therap*) or (socioenvironmental AND therap*) or (socio-environmental AND therap*) or (milieu AND therap*) or (therapeutic AND communit*) or (famil* AND therap*) or psychosoc* or psycholog* or (self AND help AND group*) or (support* AND group*) or (guide* AND image*) |
| | #4 #1 OR #2 OR #3 |

Table 01. Additional search strategies    (Continued)

| Database searched | Search strategy used |
| --- | --- |
|  | #5 DEPRESSION (MeSH) |
|  | #6 depression or depressive* or depressed |
|  | #7 #5 OR #6 |
|  | #8 NEOPLASMS (explode MeSH) |
|  | #9 tumor* or tumour* or cancer* or carcinoma* or malignan* or neoplas* |
|  | #10 #8 OR #9 |
|  | #11 #4 AND #7 AND #10 All Fields, Limits: Cancer |
|  | The above search strategy was linked to the following Cochrane filter for PubMed: |
|  | (randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized controlled trials [mh] OR random allocation [mh] or double-blind method [mh] or single-blind method [mh] or clinical trial [pt] or clinical trials [mh] or ("clinical trial" [tw] or ((singl*) [tw] or doubl* [tw] or trebl* [tw] or tripl* [tw]) AND (mask* [tw] OR blind* [tw])) OR (placebos [mh] OR placebo* [tw] OR random* [tw] OR research design [mh:noexpl]) NOT (animals [mh] NOT human [mh]) |
| PsychINFO via OVID | 1. exp PSYCHOTHERAPY/ |
|  | 2. (psychotherap$ or aromatherap$ or "art therap$" or "autogenic training" or "behavior$ therap$" or (behaviour$ adj6 therap$) or (biofeedback and psycho$) or (cognitive adj6 therap$) or (desensiti$ and psychol$) or "implosive therap$" or (relax$ adj6 therap$) or (relax$ adj6 techniq$) or (therap$ adj6 touch$) or yoga) |
|  | 3. (bibliotherap or (color$ adj6 therap$) or (colour$ adj6 therap$) or (music$ adj6 therap$) or (hypno$ adj6 therap$) or (imagery and psychotherap$) or counsel$ or (group$ adj6 therap$) or "socioenvironmental therap$" or "socio environmental therap$" or "milieu therap$" or "therapeutic communit$" or (famil$ adj6 therap$) or psychosoc$ or psycholog$ or "self help group$" or (support$ adj6 group$) or (guide$ adj6 image$)) |
|  | 4. or/1-3 |
|  | 5. exp RECURRENT DEPRESSION/ or exp REACTIVE DEPRESSION/ or exp TREATMENT RESISTANT DEPRESSION/ or exp "DEPRESSION (EMOTION)"/ or exp MAJOR DEPRESSION/ |
|  | 6. (depression or depressive$ or depressed) |
|  | 7. or/5-6 |
|  | 8. exp NEOPLASMS/ |
|  | 9. (tumor$ or tumour$ or cancer$ or carcinoma$ or malignan$ or neoplas$) |
|  | 10. or/8-9 |
|  | 11. 4 and 7 and 10 |
|  | The above subject search strategy was run with the following filter: |
|  | CCT/RCT Filter for Embase (SRB revised) |
|  | 1. (randomi$ or (control$ adj3 trial$)).mp. [mp=title, abstract, subject headings, table of contents, key concepts] |
|  | 2. ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).mp. [mp=title, abstract, subject headings, table of contents, key concepts] |
|  | 3. placebo$.mp. [mp=title, abstract, subject headings, table of contents, key concepts] |
|  | 4. exp PLACEBO/ |

**Table 01. Additional search strategies** *(Continued)*

| Database searched | Search strategy used |
|---|---|
| | 5. crossover.mp.<br>6. exp Treatment Effectiveness Evaluation/<br>7. or/1-6 |
| LILACS via www.bireme.br | ((psychotherapy OR psychotherap$ OR aromatherap$ OR (art AND therapy) OR (autogenic AND training) OR (behavior$ AND therapy) OR (behaviour$ AND therapy) OR (biofeedback AND psycho$) OR (cognitive AND therapy) OR (cognitive AND behavioural AND therapy) OR (cognitive AND behavioural AND therapies) OR (desensiti$ AND psychol$) OR (implosive AND therapy) OR (relaxation AND therapy) OR (relaxation AND therapies) OR (relaxation AND techniques$) OR (theraputic AND touch) OR (touch AND therapy) OR (touch AND therapies) OR yoga OR bibliotherapy OR (color AND therapy) OR (colour AND therapy) OR (color AND therapies) OR (colour AND therapies) OR (music AND therapy) OR hypnotherapy OR (imagery AND psychotherapy$) OR counsel$ OR (group AND therapy) OR (group AND therapies) OR (socioenvironmental AND therapy) OR (socio-environmental AND therapy) OR (milieu AND therapy) OR (therapeutic AND community) OR (family AND therapy) OR (family AND therapies) OR psychosoc$ OR psycholog$ OR (self AND help AND group) OR (self AND help AND groups) OR (support AND group) OR (support AND groups) OR (supportive AND group) OR (supportive AND groups) OR (guided AND imagery)) AND (depression OR depressive$ OR depressed OR depression) AND (neoplasms OR tumor$ OR tumour$ OR cancer$ OR carcinoma$ OR malignan$ OR neoplas$)) |

## Comparison 01. Psychotherapy versus treatment as usual

| Outcome title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 01 Depression | 6 | 517 | Standardised Mean Difference (Random) 95% CI | -0.44 [-0.80, -0.08] |
| 02 Anxiety | 5 | 411 | Standardised Mean Difference (Random) 95% CI | -0.68 [-1.37, 0.01] |
| 03 Total Mood Disturbance | 4 | 403 | Standardised Mean Difference (Random) 95% CI | -0.94 [-1.87, -0.01] |

## Comparison 02. Subgroup analyses

| Outcome title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 01 Depression | 4 | 403 | Standardised Mean Difference (Random) 95% CI | -0.58 [-1.02, -0.13] |
| 02 Anxiety | 4 | 403 | Standardised Mean Difference (Random) 95% CI | -0.77 [-1.52, -0.01] |
| 03 Total Mood Disturbance | 4 | 403 | Standardised Mean Difference (Random) 95% CI | -0.94 [-1.87, -0.01] |

## Comparison 03. Sensitivity analyses

| Outcome title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 01 Depression | 2 | 253 | Standardised Mean Difference (Random) 95% CI | -0.35 [-0.65, -0.06] |

## COVER SHEET

| | |
|---|---|
| **Title** | Psychotherapy for depression among incurable cancer patients |
| **Authors** | Akechi T, Okuyama T, Onishi J, Morita T, Furukawa TA |
| **Contribution of author(s)** | T Akechi, J Onishi, T Morita, and TA Furukawa: conceptualized and designed the study.<br>T Akechi, T Okuyama, and J Onishi: conducted the systematic review.<br>T Akechi: conducted the statistical analysis of the study.<br>TA Furukawa: supervised the process of the systematic review.<br>All authors: interpreted the data and wrote the report. |
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19

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| **Date new studies found and included/excluded** | Information not supplied by author |
| **Date authors' conclusions section amended** | Information not supplied by author |
| **Contact address** | Dr Tatsuo Akechi<br>Associate Professor<br>Department of Psychiatry<br>Nagoya City University Medical School<br>Mizuho-cho, Mizuho-ku<br>Nagoya<br>Aichi<br>467 8601<br>JAPAN<br>E-mail: takechi@med.nagoya-cu.ac.jp<br>Tel: +81 52 853 8271<br>Fax: +81 52 852 0837 |
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## Figure 01. Funnel plot for the outcome depression

Review:        Psychotherapy for depression among incurable caner patients
Comparison:  01 Psychotherapy versus treatment as usual
Outcome:      01 Depression

## Figure 02.   Funnel plot for the outcome anxieety

Review:        Psychotherapy for depression among incurable caner patients
Comparison:  01 Psychotherapy versus treatment as usual
Outcome:     02 Anxiety
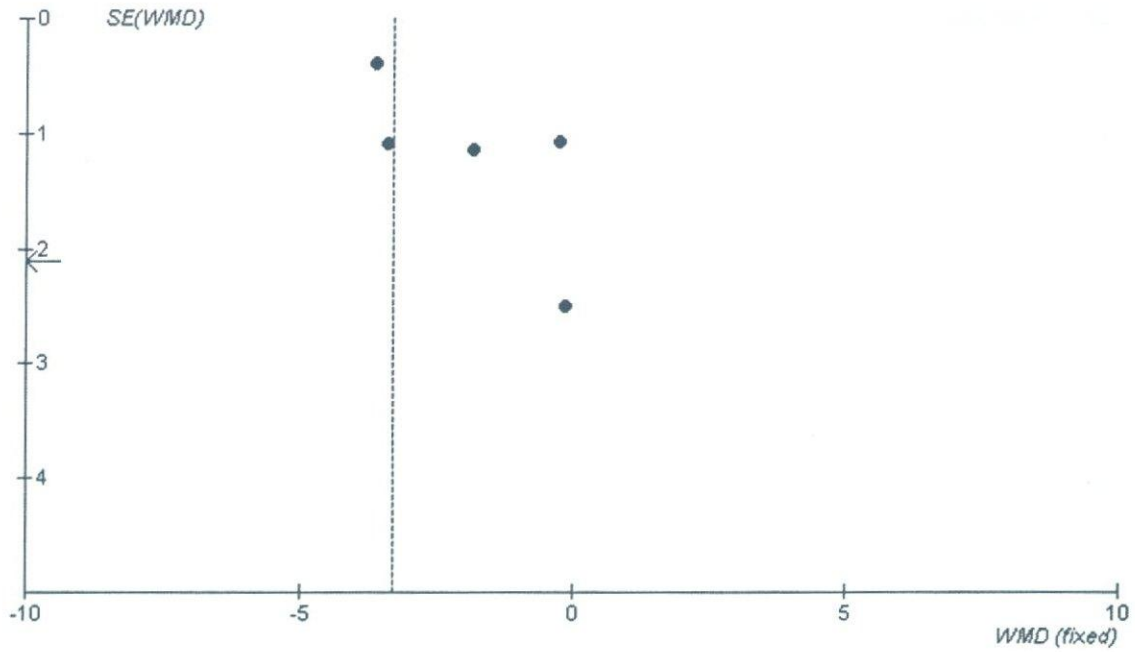
**Figure 03.   Funnel plot for the outcome total mood disturbance**

Review:        Psychotherapy for depression among incurable caner patients
Comparison:  01 Psychotherapy versus treatment as usual
Outcome:      03 Total Mood Disturbance
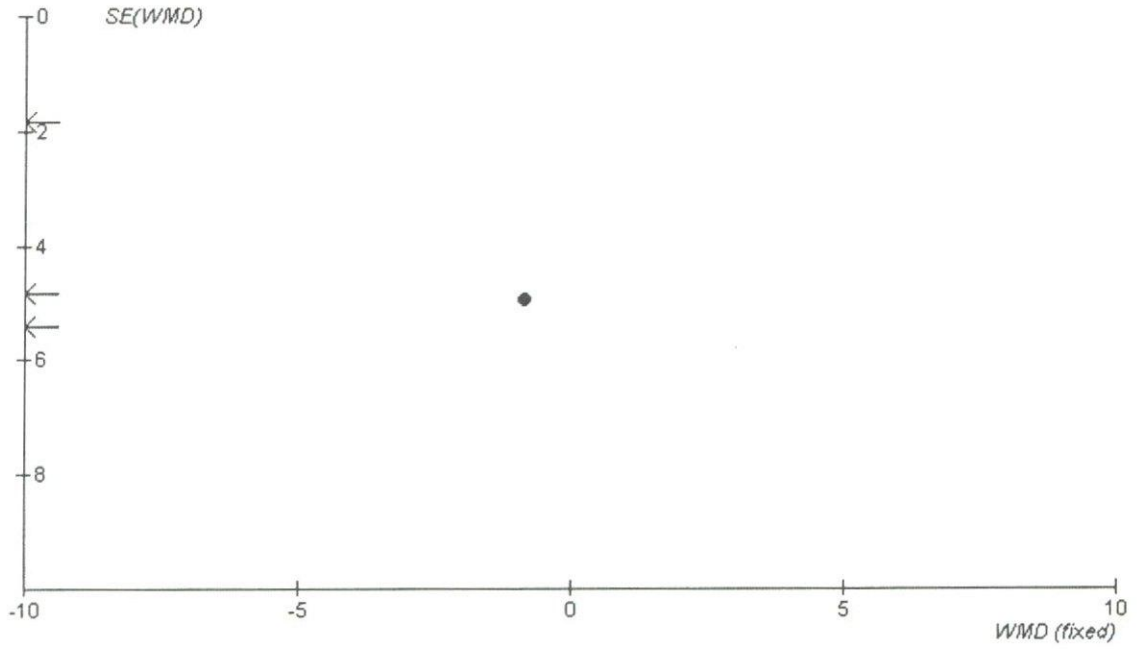
## Analysis 01.01.   Comparison 01 Psychotherapy versus treatment as usual, Outcome 01 Depression

Review:   Psychotherapy for depression among incurable cancer patients

Comparison:   01 Psychotherapy versus treatment as usual
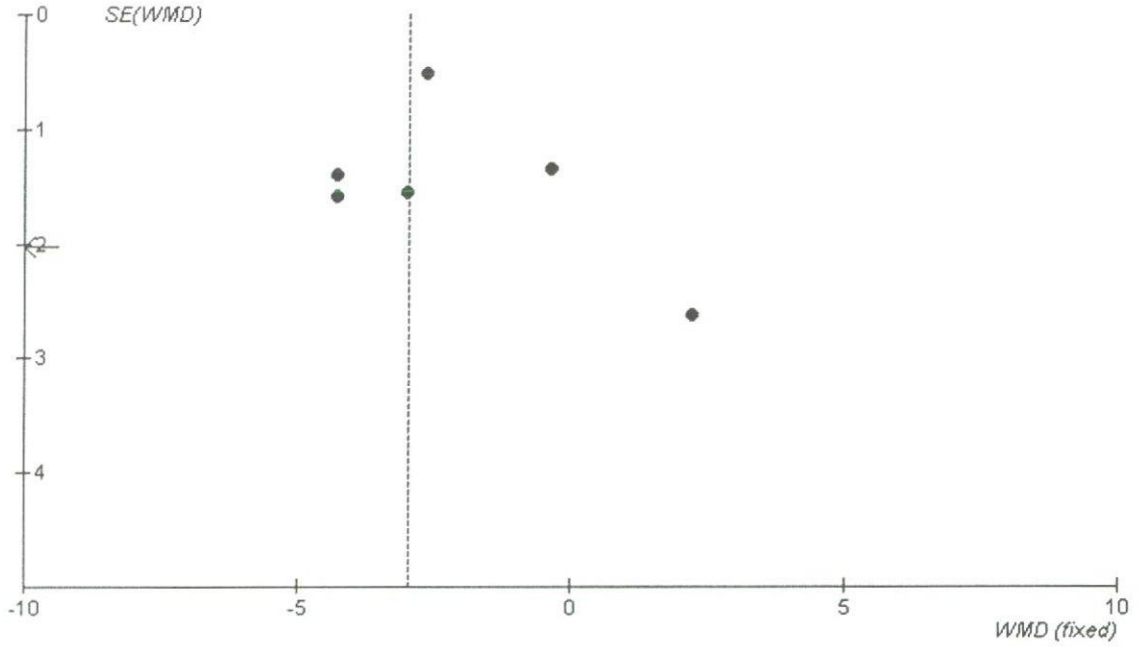
Outcome:   01 Depression

| Study | Treatment | | Control | | Standardised Mean Difference (Random) 95% CI | Weight (%) | Standardised Mean Difference (Random) 95% CI |
|---|---|---|---|---|---|---|---|
| | N | Mean(SD) | N | Mean(SD) | | | |
| Classen 2001 | 58 | -1.80 (7.94) | 44 | -1.44 (6.38) | | 19.7 | -0.05 [ -0.44, 0.34 ] |
| Edelman 1999 | 43 | -3.07 (7.91) | 49 | 1.22 (7.24) | | 19.1 | -0.56 [ -0.98, -0.14 ] |
| Goodwin 2001 | 102 | -1.70 (9.20) | 45 | 2.60 (7.10) | | 20.6 | -0.50 [ -0.85, -0.14 ] |
| Linn 1982 | 50 | -1.00 (7.94) | 56 | 0.40 (6.38) | | 19.9 | -0.19 [ -0.58, 0.19 ] |
| Spiegel 1981 | 34 | -0.12 (1.75) | 28 | 2.52 (2.22) | | 16.0 | -1.32 [ -1.87, -0.76 ] |
| Wood 1997 | 5 | 0.20 (2.77) | 3 | -2.00 (4.00) | | 4.8 | 0.59 [ -0.90, 2.08 ] |
| **Total (95% CI)** | **292** | | **225** | | | **100.0** | **-0.44 [ -0.80, -0.08 ]** |

Test for heterogeneity chi-square=17.29 df=5 p=0.004 I² =71.1%

Test for overall effect z=2.40   p=0.02

```
        -4    -2    0    2    4
   Favours treatment    Favours TAU
```

## Analysis 01.02.   Comparison 01 Psychotherapy versus treatment as usual, Outcome 02 Anxiety

Review:   Psychotherapy for depression among incurable cancer patients

Comparison:   01 Psychotherapy versus treatment as usual
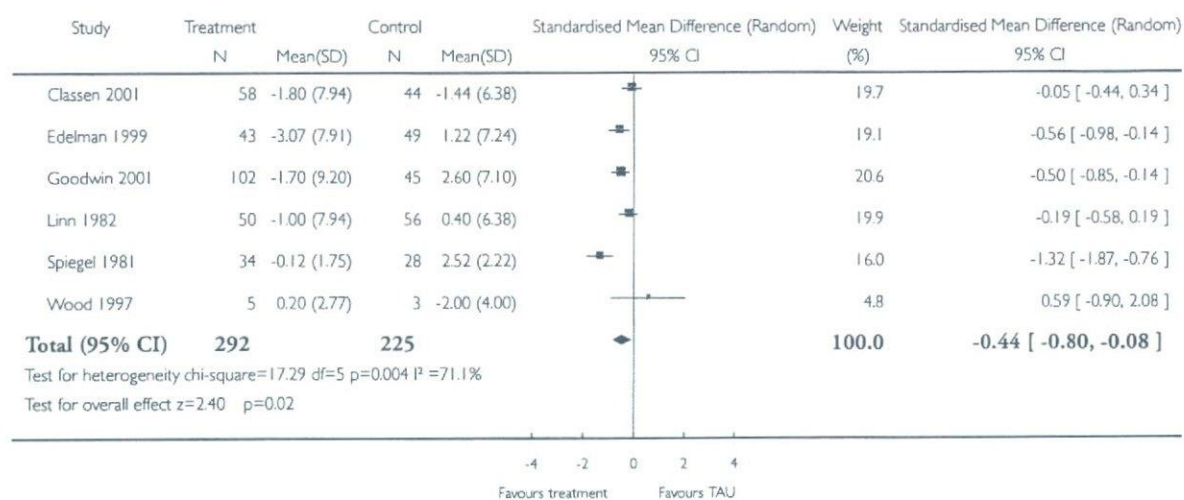
Outcome:   02 Anxiety

| Study | Treatment | | Control | | Standardised Mean Difference (Random) 95% CI | Weight (%) | Standardised Mean Difference (Random) 95% CI |
|---|---|---|---|---|---|---|---|
| | N | Mean(SD) | N | Mean(SD) | | | |
| Classen 2001 | 58 | -0.60 (5.80) | 44 | -0.36 (5.05) | | 22.7 | -0.04 [ -0.44, 0.35 ] |
| Edelman 1999 | 43 | -1.53 (5.20) | 49 | 0.29 (5.72) | | 22.5 | -0.33 [ -0.74, 0.08 ] |
| Goodwin 2001 | 102 | -1.50 (6.90) | 45 | 1.90 (5.70) | | 23.0 | -0.52 [ -0.87, -0.16 ] |
| Spiegel 1981 | 34 | -2.73 (1.28) | 28 | 0.87 (1.75) | | 20.0 | -2.35 [ -3.01, -1.70 ] |
| Wood 1997 | 5 | 0.20 (4.09) | 3 | 0.33 (5.13) | | 11.9 | -0.03 [ -1.46, 1.41 ] |
| **Total (95% CI)** | **242** | | **169** | | | **100.0** | **-0.68 [ -1.37, 0.01 ]** |

Test for heterogeneity chi-square=36.77 df=4 p=<0.0001 I² =89.1%

Test for overall effect z=1.92   p=0.05

```
        -4    -2    0    2    4
   Favours treatment    Favours control
```